INTRODUCTION TO GENERAL PHARMACOLOGY

- It is classified into two major types – Pharmacokinetics and Pharmacodynamics.
- Pharmacokinetics is the study of movement of drug within the body.
- Pharmacodynamics is the relationship between drug concentration and drug action in the body.

Pharmacokinetics 00:04:56

- It can be of four types:

i. Absorption – Movement of drug from site of administration to the blood.

ii. Distribution – Phenomenon of breakdown of drug molecules from blood to target tissues or organs.

iii. Metabolism – Phenomenon of breakdown of drug molecules from blood to metabolizing organ.

iv. Excretion – Movement of drug molecules from blood outside body most commonly urine.

- After administration of the drug, the drug molecules move into the intestine (after oral)
- From the intestines, the drug is absorbed into the blood.
- Once the drug is distributed and moves into the tissues, it leads to tissue storage.

- It binds with the target enzymes and forms the necessary actions.
- The drug gets metabolized after its action has been finished.
- Finally, the drug gets excreted out.
- A step occurs before pharmacokinetics called drug dissolution and disintegration of the oral formulation. The study of this phase is called pharmaceutical phase.

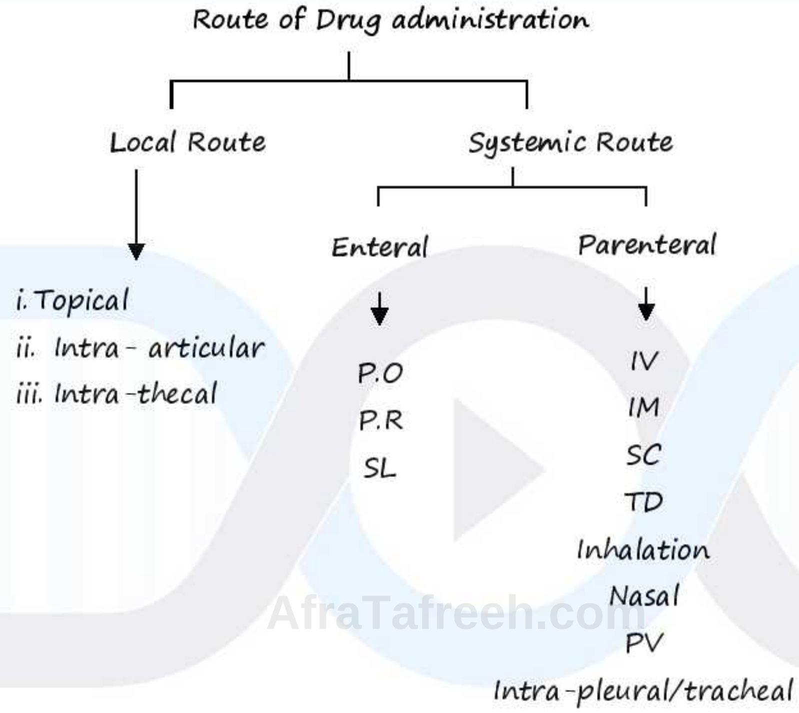
- Plasma concentration vs Time plot:
  - In a volunteer, a single dose of drug is administered and blood is withdrawn periodically and sent for biochemical analysis.
  - In the biochemical analysis - the number of milligrams of drug in blood is analyzed.
  - The maximum concentration which the drug attains in the plasma is called C max.
  - The time taken for attaining the maximum concentration is called T max.
  - Minimum therapeutic concentration is the minimum plasma concentration of a drug needed to achieve a desired pharmacologic response.
  - The time when drug starts shows its effects after administration the drug effects are seen is called onset of action.
  - The duration of action is the time duration in which the drug produces the action in the human body.

- The area under the curve is calculated with linear / log trapezoidal curve.
- Area under the curve explains the extent of absorption/availability of drug in systemic circulation.
- C max is the maximum concentration of drug attained in the plasma.
- T max is the time taken for C max. It indicates the rate of absorption.
- T max is inversely proportional to the rate of absorption.

DRUGS ABSORPTION

- Site of Administration → Blood

Route of drug administration 00:02:10


Route of Drug administration
Local Route
Systemic Route
Enteral
Parenteral
i. Topical
ii. Intra - articular
iii. Intra -thecal
P.O
P.R
SL
IV
IM
SC
TD
Inhalation
Nasal
PV
Intra-pleural/tracheal

DOI TUTORIALS
LOGIC FOR SUCCESS

i. Topical Route:

- Drugs with more systemic toxicity

ii. Intra-articular:

- Hyaluronidase (viscosupplementation)
- Steroids
- Platelet rich plasma

iii. Intra-Thecal:

- Drugs not crossing the Blood Brain Barrier (BBB)

Systemic Route 00:10:13

i. P.O – (Enteral route)

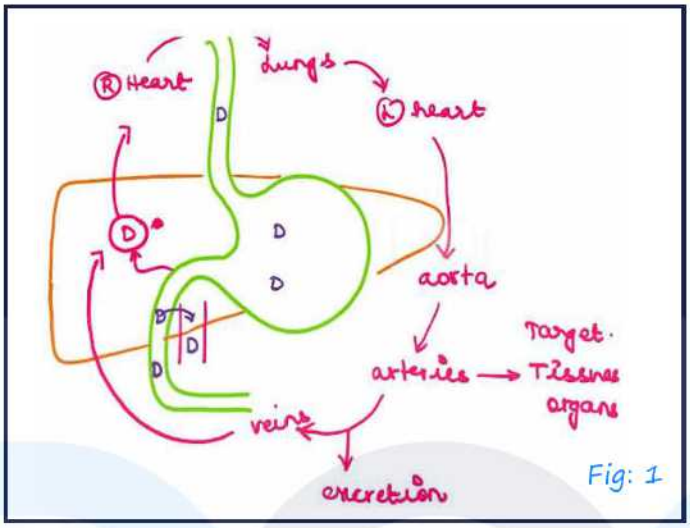
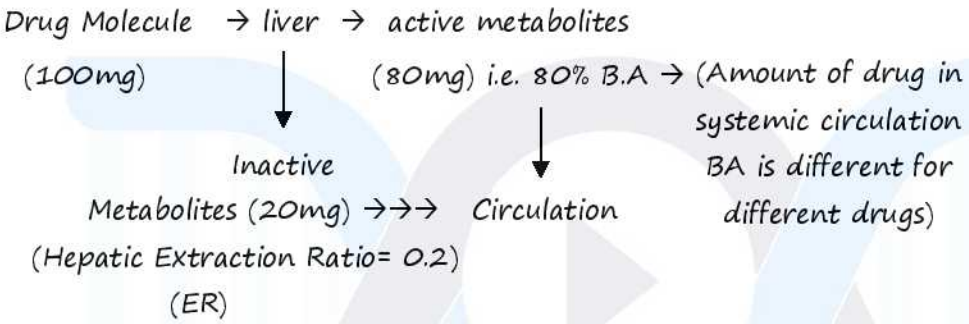


Fig: 1

- Safer, economical can be self-administrated
- When any drug is administered, it enters stomach → to intestines and then to the blood vessels (absorption)
- Then the drug gains entry into the Liver → Right chamber of Heart → Lungs → left chamber of heart → moves out through aorta → moves to arteries → target tissues / organs
- From arteries the drug enters veins → back to liver
- In the above cyclic path, the drug gets metabolised in the liver
- The drug molecule gets ionised so as to get dissolved in water. This conversion is called metabolism
- First pass metabolism → also called pre-systemic metabolism is the metabolism/breakdown of the dry

before it reaches systemic circulation or blood. It can take place in liver or GI tract

- Only the active part (say 80%) of the drug gets circulated back into the system. The inactive part (balance 20%) gets excreted.
- In the second pass metabolism the active part of the drug gets metabolised again


Drug Molecule → liver → active metabolites
(100mg)
(80mg) i.e. 80% B.A → (Amount of drug in systemic circulation BA is different for different drugs)
Inactive Metabolites (20mg) →→→ Circulation
(Hepatic Extraction Ratio= 0.2)
(ER)

$$\text{Thus B.A } (F) = \underline{f \times (1-ER)}$$

f fractional absorption

ER Extraction ratio

-This Bio availability of any drug can be increased if it is given as micro fine particles. E.g., of drugs:

- Aspirin
- Griseofulvin
- Spironolactone

ii. P.R (Enteral Route)

- First pass metabolism (FSM) is decreased upto 50%
- Primary importance of P.R is to bypass Nausea and Vomiting

iii. SL (Enteral Route)

Highly lipid soluble

Parenteral Route 00:25:32

- IV → 100% B.A
- IM → Large molecules & Smaller molecules

  ↓ ↓

  Has to be lipid soluble   Enter blood through pores

- Water soluble large molecules administered through IM route do not get absorbed – get accumulated in that area e. g: Heparin

  (CI – IM) causes Hematoma

- Sub-Cutaneous (in SC + Hyaluronidase → increases absorption)
- Transdermal
- Inhalation Route → faster onset of action
- Intra-nasal route →
  - i. Desmopressin
  - ii. Calcitonin
  - iii. Nafarelin
  - iv. Afrezza (intra nasal insulin)
  - v. Etripamil (CCB → SVT)
  - vi. Oxymetazoline

Movement of small drug molecules across bio membranes 00:34:35

- There are three major routes -
  1. Passive / Simple diffusion
  2. Facilitated diffusion
  3. Active transport

Transport	Gradient	Energy	Carrier
Passive/Simple diffusion	Down the gradient	No energy required	Not necessary
Facilitated diffusion	Down the gradient	No energy required	Required
Active transport	Against the gradient	Energy required	Required

Passive diffusion

- Drug molecule is secreted into breast milk via passive diffusion

Facilitated diffusion

- GLUT 4 - Do not utilize energy.
- Solute carrier transporters (SLC molecules)

Active transport

- Two types - primary and secondary.

Primary

- It involves active efflux pump.
- Example - P Glycoprotein molecules, Multi drug resistant type 1 proteins, Multi drug resistance associated proteins, Breast cancer resistant carrier proteins.

Secondary

- It includes organic anion transporter or organic cation transporter, norepinephrine transporter, dopamine transporter, VMAT.

Ionization 00:44:01

- Majority of drugs given are weak acid or weak base molecules to prevent corrosive damage
- Henderson–Hassel Bach's equation - The percentage between the ionized and unionized complex
- Equilibrium is maintained whenever we administer a weak acid or weak base
- Ionized drugs are impenetrable whereas unionized drugs are penetrable
- Ionized drugs are water soluble and unionized drugs are lipid soluble

Weak acid v/s weak base 00:44:01

Weak Acid	Weak Base
Acidic drug + Acidic medium = Unionized complex	Basic drug + Basic medium = Unionized complex
Acidic drug + Basic medium = Ionized form	Basic drug + acidic medium - Ionized form
Absorption - Maximum in stomach but practically in intestines due to mucus membrane, surface area, vascularity.	Absorption - Maximum in basic medium - intestines
Interact with cations	Interact with anions
Example - Phenytoin sodium, Thiopentone sodium, Diclofenac sodium, Potassium Penicillin V	Example - Morphine sulphate, Protamine sulphate,

- Any drug which increases gastric emptying - Increases absorption of drugs. pH independent absorption - Seen in alcohol
- **Bio equivalence means** – similarity of two drugs (from the same group) from two different pharmaceutical companies.

Drugs with high BA/100% BA:

- i. Warfarin
- ii. Nizatidine
- iii. Isosorbide mononitrate
- iv. Oxazolidinones
- v. Levofloxacin

Drugs which have high first pass metabolism

- i. Morphine
- ii. Verapamil
- iii. Salbutamol
- iv. Alprenolol
- v. Propranolol
- vi. Glyceryl trinitrate
- vii. Pethidine

DRUGS DISTRIBUTION

Definition 00:00:13

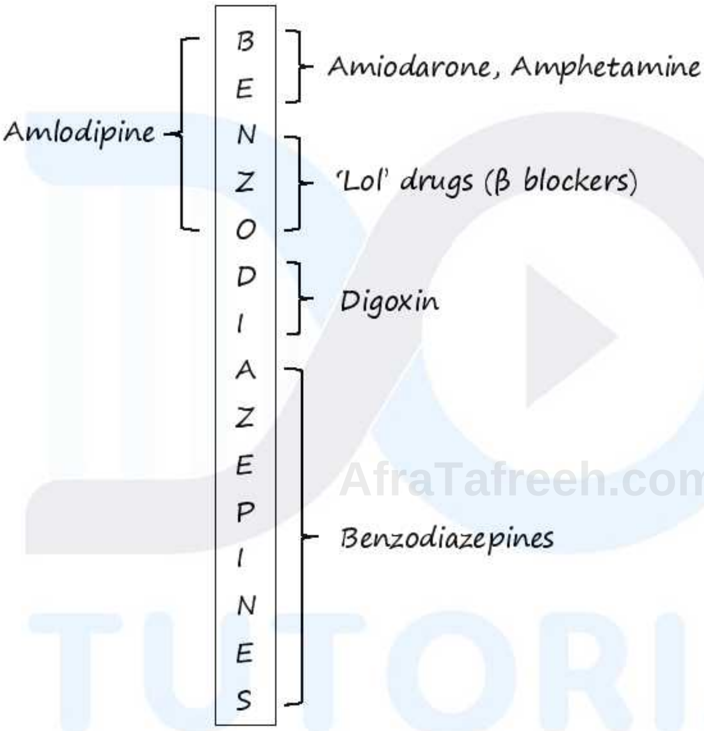
- Movement of drug molecule from blood to target tissue/ organs.
- Free drug/ active form of drug binds to protein in blood and form equilibrium with drug protein complex.
- Free ⇋ drug + protein (Drug protein complex).
- Bound drug is inactive that is more amount of drug bound to plasma protein means less amount of drug in active from. Hence plasma proteins are called sites of loss/silent receptor's/ drug acceptors.
- If a drug is highly plasma protein bound it has
  - Increased drug interaction → displacement reaction.
  - Increased duration of action due to decrease glomerular filtration.
  - Decreased volume of distribution (decreased Vd), Drug remains in vascular compartment.
- Displacement reaction example → when warfarin and aspirin are administered together, aspirin having higher affinity for plasma proteins displace bound warfarin. This leads to high count of active/ free warfarin leading to toxicity.
- Displacement reaction not seen.
  - Between acid/ basic

  - Between probenecid/ Indomethacin.
- Distribution depends on
  - Blood flow
  - Volume of distribution (vd)
- Plasma protein binding
  - Acidic drugs bind to albumin
  - Basic drugs bind to globulin
- Blood flow → organs which receive high blood flow are the organs to which the drug will arrive faster.
  - Brain, liver, Kidney > muscle, skin > Fat and bone
- Vd → volume of bodily fluid in which drug gets distributed.
- Clearance → the volume of bodily fluid from which the drug is removed out per unit time.
- Dose administered = concentration of drug in plasma (cp) * volume of distribution (vd)
  - Concertation of drug in plasma is not constant due to metabolism and excretion so Cp is changed to Co (initial plasma concentration).
- Vd is directly proportional to
  - Volume → Gets distributed (L)

$$Vd = \frac{\text{Dose administered}}{Co}$$

  - Age
  - Obesity
  - Lipid solubility of drug

  - Pregnancy
- Vd is inversely proportional to plasma protein binding.
- Vd → more in females than males.
- High Vd means more drug in tissues.
- Drugs with high Vd
  - Chloroquine
  - Mnemonic "Benzodiazepines"


B
E
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S
Amiodarone, Amphetamine
Amlodipine
'Lol' drugs (β blockers)
Digoxin
Benzodiazepines

  - Organophosphorus compounds
- If a drug has Increased Vd →
  - It will have increased D.O.A
  - In case of poisoning, hemodialysis is least effective.

Redistribution 00:28:56

Drug administered

↓

Absorption

↓

Distribution to organ A

↓

More tissue binding property (highly lipid soluble)

↓

Distributed to organ B

↓

As plasma concentration decreased

↓

Movement of drug from organ A to B (Redistribution)

[Blood, liver, kidney]

- Redistribution phenomenon seen with highly lipid soluble drugs, CNS active drugs. It is not seen with all drugs.
- E. g: - Thiopentone sodium, Diazepam and Nitrazepam.
- Termination of action of thiopertone sodium is because of redistribution more than metabolism. This is also seen with
- Enzymatic blood brain barrier

Capillary walls of brain have enzymes

↓

Monoamine Oxidase(MAO) & acetylcholine esterase (ACGE)

↓

Prevents entry of mono amines into brain

- Hoffman elimination → It is non enzymatic degradation after which the drug is excreted.
  - E. g: – Atracurium (It can be given in liver and renal failure)

- Selective distribution

  E.g. – Phenothiazine] High volume of distribution

  Chloroquine] but binds to selective areas.

  - Phenothiazine & chloroquine → binds selectively to melanin containing tissue [retina]

    e.g. – Iodine → binds selectively to thyroid [specialized transport]

DOT TUTORIALS
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PHARMACODYNAMICS PART – I

- Drug molecule interacts with the target proteins and it can cause therapeutic effect or adverse effects.
- Target proteins can be of three main types –

  i. Receptors

  ii. Enzymes

  iii. Transporters

Transporters

- Tricyclic antidepressants / SSRI target SERT transporters.
- Amphetamine blocks dopamine transporter.
- Reserpine targets VMAT – 2 transporter.
- Tiagabine targets GABA – T transporter.
- Furosemide / Thiazide $Na^+ - K^+/2cl^-$
- Thiazide targets $Na^+ - Cl^-$ transporter symporter molecular
- Probenecid targets organic acid transporter and increases its activity.

Receptors 00:04:57

- They transmit impulses from a drug or a neurotransmitter into the particular nucleic acid so that more or a smaller number of proteins are synthesized.

- The receptors can be classified by location –

  1. Cell surface adhesion receptors
  2. Transmembrane receptors –

- There are three types –
  - a. Linked to G proteins.
  - b. Linked to enzymatic domain.
  - c. Ionic channels.

  3. Intracellular receptors –

- There are two types –
  - a. Cytoplasmic
  - b. Nuclear

Cell surface adhesion receptors 00:06:10

- In case of bleeding, we need adhesion of platelets.
- In case of infection or antigen, the immune system needs to adhere with itself to increase the response.
- This group of receptors are also called integrin receptors.
- They are blocked by Glycoprotein II b / III a receptor inhibitor – Abciximab, → Non – selective Tirofiban, and Eptifibatide. → Selective

Transmembrane receptors 00:08:30

Ionic channels

- They are also called Cys – loop receptors.

- They are the fastest acting channels and cause an immediate response within milliseconds.
- Example – Nicotinic channels, GABA A, Glycine, Glutamate, Purinergic.

Channel	Ions
Nicotinic	Controls sodium ions
GABA A	Controls chloride ions
Glycine	Controls chloride ions
Glutamate	Controls sodium or calcium ions
Purinergic	P1 and P2Y are G protein coupled receptors. P2X is an ionic channel.

Structure of receptors – Nicotinic receptor

- The cellular membrane has a gap on the surface.
- The membrane structure is surrounded by 5 different subunits.
- In the Centre there is a gamma subunit.
- On the sides there are two alpha subunits.
- Behind there are beta and delta subunits.
- Once the gamma subunit is ripped off, the alpha subunits are present.
- The alpha subunit has a kink on the M2 segments.
- For opening of this particular channel, we need binding of two major types of acetylcholine

molecules to bind with the alpha subunits so that sodium influx can occur.

- There are three types of ionic channels -

  i. Ligand gated

  ii. Voltage gated

  iii. 2nd messenger regulated

G protein coupled receptors 00:15:07

- They are also called amplification receptors.
- Examples - Muscarinic receptors, Adrenoceptors, Dopaminergic receptors, Serotonergic receptors (Except 5HT3), odorant receptors

Mechanism of action

- In the membrane, the extracellular domain passes through 7 times.
- The intracellular domain has a protein called G protein.
- G protein has three subunits - beta, gamma, alpha.
- At rest, alpha is bonded with GDP.
- Enzymes on the surface are called effector organs -

  i. Adenylyl cyclase

  ii. Phospholipase C

  iii. Mitogen Activated Protein Kinase (MAPK)

  iv. Rho kinase/Rho – A kinase (P kinase/P.A kinase)

  v. Ionic channels

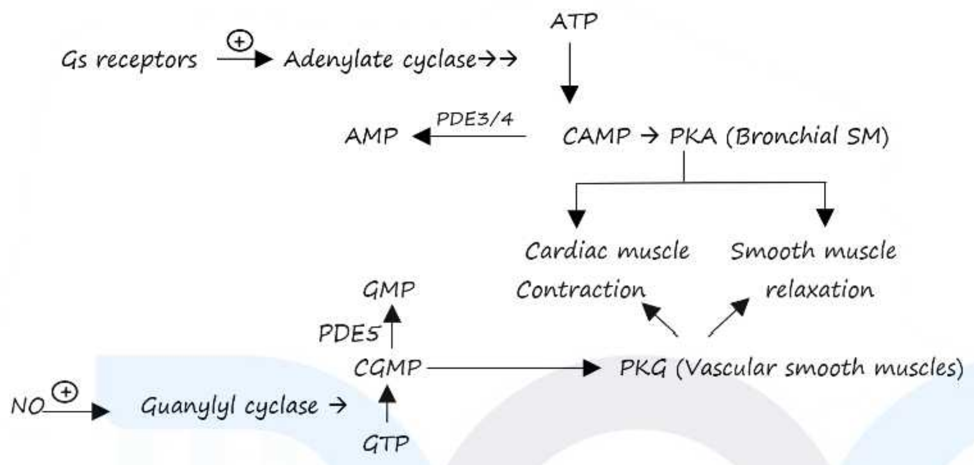
- Whenever there is agonist binding, alpha GDP is converted to alpha GTP and it dissociates from beta gamma subunits.
- Alpha GTP binds with effector organs and it might activate or inhibit based on the type of protein.
- The effector organ releases 2nd messengers.
- On agonist unbinding, alpha GTP is converted to alpha GDP due to intrinsic GTA – as activity of alpha.
- Alpha GDP binds with beta gamma subunits.
- Finally, it moves into rest position.

Types of G protein coupled receptors 00:23:49

Types	Classification
Gs	Gs1, Gs2
Gi	Gi1, Gi2, Gi3
Gq	
Gz	Seen in brain
GO	
G 12/13	Effector organ is ionic channel

PHARMACODYNAMICS PART – II

Gs coupled receptors 00:00:06


Gs receptors
⊕
Adenylate cyclase
ATP
AMP
PDE3/4
CAMP → PKA (Bronchial SM)
Cardiac muscle Contraction
Smooth muscle relaxation
GMP
PDE5
CGMP
PKG (Vascular smooth muscles)
NO
⊕
Guanylyl cyclase
GTP

Examples of Gs coupled receptors

- All beta receptors (beta$_1$, beta$_2$, beta$_3$)
- Dopamine → D$_1$
- Serotonin → (5HT4,6,7)

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Drugs that inhibit

PDE 3 inhibitors

- Cilostazol (intermittent claudication)
- Milrinone
- Inamrinone
- Vesnarinone

Milrinone, Inamrinone, Vesnarinone – Indicators [CCF-acute]

PDE 4 inhibitors

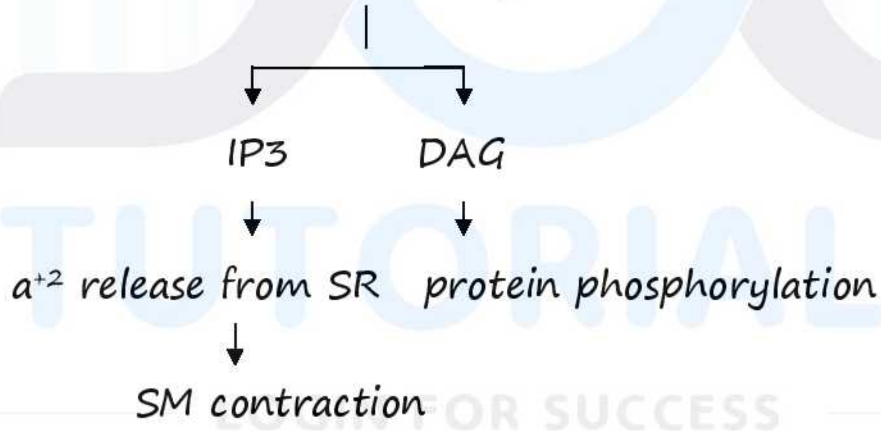
- Roflumilast (COPD)

- PDE 3&4 inhibitors
  - Methylxanthines → Theophylline, caffeine (@high doses) [Adenosine receptor antagonist@ therapeutic doses]

- Guanylyl cyclase is activated Nitric oxide (NO) which is a potent endogenous vasodilation.
- Drugs that increase NO
  - i. Nitrates
  - ii. Nitroprussides
  - iii. Hydralazine
  - iv. Bradykinin
- PDE – 5 inhibitors → Sildenafil Tadalafil etc.
- Direct Guanylyl cyclase directly → Riociguat (used in R_x of pulmonary artery hypertension (PAH)

Gq coupled receptors 00:08:50

Gq $\xrightarrow{\oplus}$ Phospholipase C → Phosphatidylinositol diphosphate



- Any Gq receptors causes SM contraction.

Examples of GQ receptors

- 7 pass transmembrane receptors
- Majority of GI are presynaptic (also postsynaptic)
- Gi inhibits Adenylyl cyclase.

Examples of Gi receptors

If Ach is the neurotransmitters
↓
M_2, M_4

If noradrenaline or adrenaline is the neurotransmitters
↓
alpha2

If Dopamine is the neurotransmitters
↓
D_2, D_3, D_4

If Serotonin is the neurotransmitters
↓
$5HT_1$, $5HT_2$

If Histamine is the neurotransmitters → H_3, H_4

Go receptors

- Go receptors inhibit calcium release (action opposite to that of GQ receptors)

Receptors linked to Enzymatic domain 00:13:00

Enzymatic domain

Linked to tyrosine kinase
- GH
- Insulin

Linked to membrane bound Guanylyl cyclase
- Natriuretic peptide receptor

linked to serine-threonine kinase
- TGF- beta

Jak – STAT receptors (Janus kinase – signal transducer & activator of transcription)

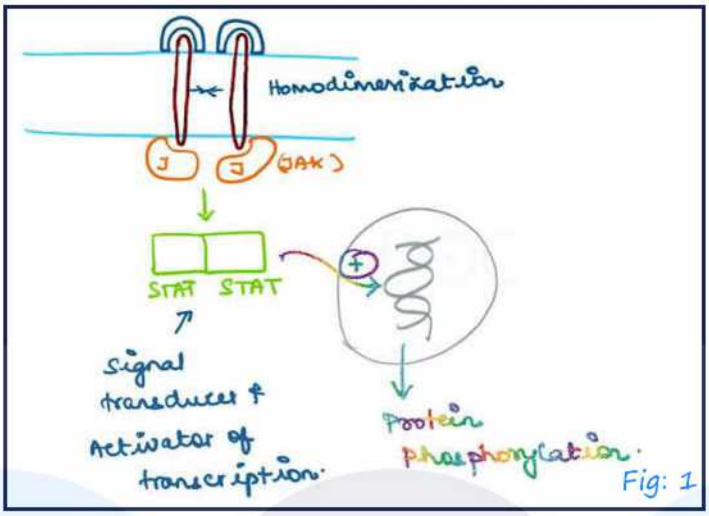

Homodimerization
J
J
(JAK)
STAT STAT
+
signal transducer & Activator of transcription.
Protein phosphorylation.

Fig: 1

- Both the receptor domains are separated. In order to activate the intracellular proteins, these domains should fuse together.
- The intracellular domain is the JAK proteins and the extracellular domain is either occupied by neurotransmitters or drugs.
- Fusion of both the receptors domains is called as Homodimerisation.
- The intracellular proteins that are activated as a result of fusion of receptor are called → STAT proteins → signal transducer & activator of transcription
- STAT proteins that are activated go the nucleus & activate transcription → and there is resultant protein phosphorylation.

Intracellular receptor 00:17:06

Intracellular receptor

Cytoplasmic receptors
- Androgen
- Corticosteroids

Nuclear receptors
- T_3 T_4
- Retinoic acid
- Vit. D_3

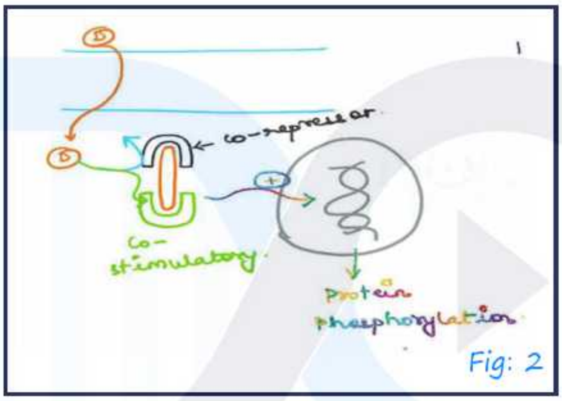


Fig: 2

- Receptor inside the cell is inhibited during the inactive stage by co-repressor molecules.
- Drug that was administered gains entry into the cell, removes co-repressor molecule and adds co-stimulatory molecule.
- The co-stimulatory molecule now enters nucleus → Transcription → protein phosphorylation.

Types of intracellular receptors

i. PPAR – α (Alfa → All fat → hypolipidemic agent) ⊕← Fibrates.

ii. PPAR – γ (Gamma → Glucose → Hypoglycemic agent) ←⊕ pioglitazone.

Drug – Receptor interaction 00:21:52

- Affinity
↓
Strength of binding of receptor is called affinity.
↓
Strength of association

- Intrinsic activity
↓
The reaction of an organ due to affinity of the drug to the receptor (Activation of receptor and generation of response)
↓
Maximal functional response

	Affinity	Intrinsic activity
i. Agonist	+	+1
ii. Partial agonist	Increased	0 to +1
iii. Antagonist	+	0
iv. Inverse agonist	+	0 to −1

Partial agonistic agents

i. Varenicline → partial agonist Nicotinic receptor → used for smoking cessation. While treating smoking cessation, antagonist is not given as the smooth muscle activity is opposite (zero intrinsic activity) to that of smoking. Whereas, and inverse agonist agent (zero to −1 intrinsic activity) causes exaggerated symptoms.

ii. Buprenorphine → partial agonist @ μ (mu) receptor → used for opioid withdrawal.

iii. Aripiprazole → partial agonist @D_2 & $5HT_{1A}$

Inverse agonistic agents

i. Beta – Carboline → inverse agonist @ GABA receptors

→inverse agonist @ pro convulsive agent

ii. Rimonabant → inverse agonist @ cannabinoid receptor (CB_1) → decreases the appetite → Anti-obesity agent → banned because of neuropsychiatric symptoms.

PHARMACODYNAMICS PART III

Based agonist 00:00:02

- Produces 2 types of responses when stimulating the receptor
  - i. Gi- mediated signaling
  - ii. β – Arrestin mediated signaling
- Commonly seen in opioids & serotonin
- In opioids = Gi- Mediated response: Analgesia
- β- arrestin mediated signaling
  - i. Respiratory depression
  - ii. Constipation

Spare receptors 00:01:33

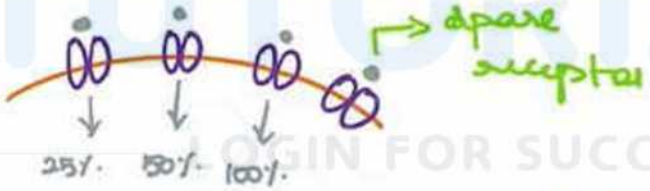


Fig: 1

- Receptor in excess of required amount (of neurotransmitter) to produce maximal functional response
- If does not affect/alter maximal efficacy
- It alters sensitivity of the drug
- Indicator of spare receptor When $EC_{50} < Kd$
- Kd – Dissociation constant

- EC_{50} effective concentration in 50% of population

Enzyme & Drug Interaction 00:04:37

Competitive Inhibitors

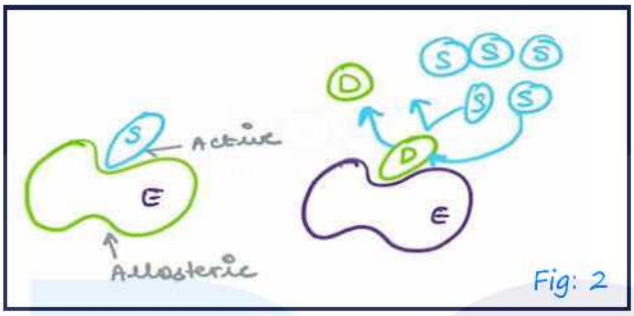


Fig: 2

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- Compete with Substrate (S) molecule for the active site of the enzyme
- If the one molecule of substrate (Say S1) Senses competitive CI inhibitors presence at the active site, it will move away
- However, if there are multiple S Molecules (S2, S3, S4) they will attach to the CI at the active site & actually throw out the CI
- Where does CI bind? Active site of enzyme
- What if the concentration of substrate increases? Then it becomes **surmountable** & CI can be thrown out

Noncompetitive inhibitors 00:09:34

- Binds at allosteric site resulting in change of structure of active molecule

- As the structure itself is altered, an increase in concentration will make no difference
- What if concentration increases? Remains insurmountable

Reversible

- Comp inhibitors

Irreversible Organo-phosphorous of Acetylcholinesterase, Methotrexate of dihydrofolate reductase

Non-Competitive inhibitors

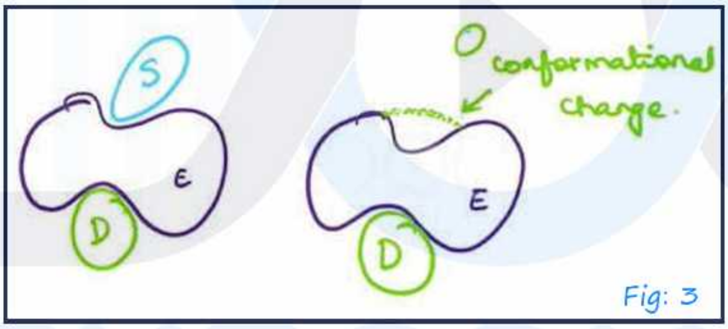

Fig: 3

- Competitive inhibitors only preclude further interaction of substrate with enzyme
- Non comp inhibitors actually reverse action
- Noncompetitive inhibitors bind to both enzyme and enzyme-substrate complex
- Binds where ? : Allosteric site of both enzyme and enzyme-substrate complex causing conformational change
- as a result of binding to two sites, also called 'mixed inhibitors'

- S molecule is denied blinding with active site
- Change is seen not only with a) enzyme but also with b) enzyme – Substrate complex
- As a result, S molecule is definitely thrown out

Choice of drug

a. Depending upon whether you want reversal of action or prevention of further interaction

b. Concentration

- To revise,

a. Binds where?
  - Allosteric site of enzyme
  - Enzyme – Substrate (E-S) complex

- Hence called mixed inhibitors

b. What if Conc. Increase? – No change and unsurmountable

- Hence, they are irreversible (Mostly)
- Exceptions – Ticagrelor (P2Y12 Inhibitor)
- Non comp Inhibitors
  - Irreversible Clopidogrel
  - Reversible Ticagrelor & Carbonic anhydrase inhibitors

Uncompetitive inhibitors

- Does not bind to the enzyme

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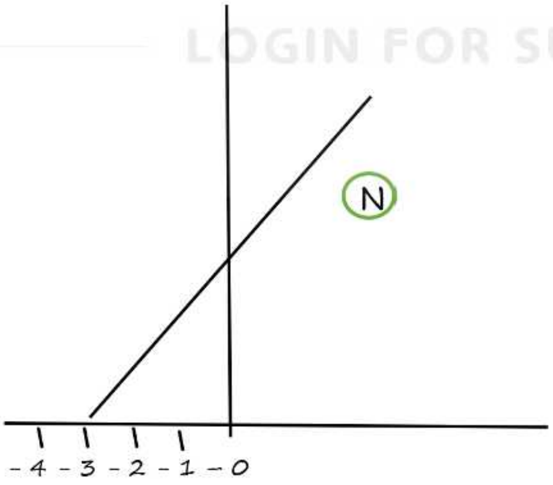
- Binds only to Enzyme-Substrate (E-S) complex
- H is a single entity inhibitor
- H also binds with enzymes with multiple substrate binding pockets
- E.g. Lithium
- Lithium is an uncompetitive inhibitor of
  i. Inositol monophosphatase IMPase
  ii. Glycogen synthetase kinase GSK – ase

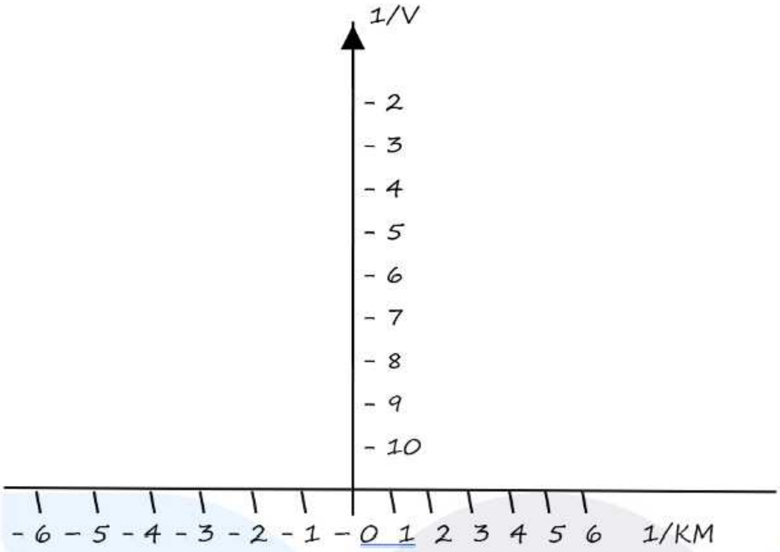
Vmax & Km

- Vmax – Maximal velocity of reaction between enzyme & substrate
- K_m – Concentration of substrate required for producing ½ Vmax

Lineweaver burk plot 00:15:55



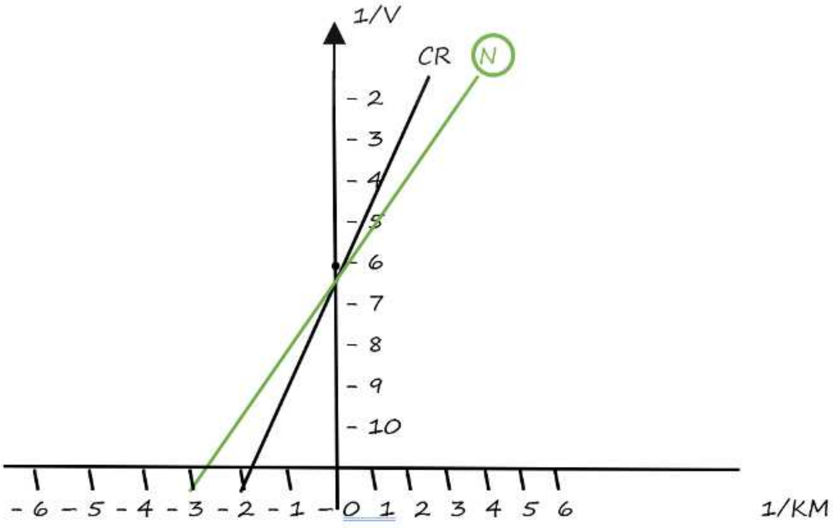
Normally this how a L-B plot looks



Competitive reversible

i. CR – RSXY

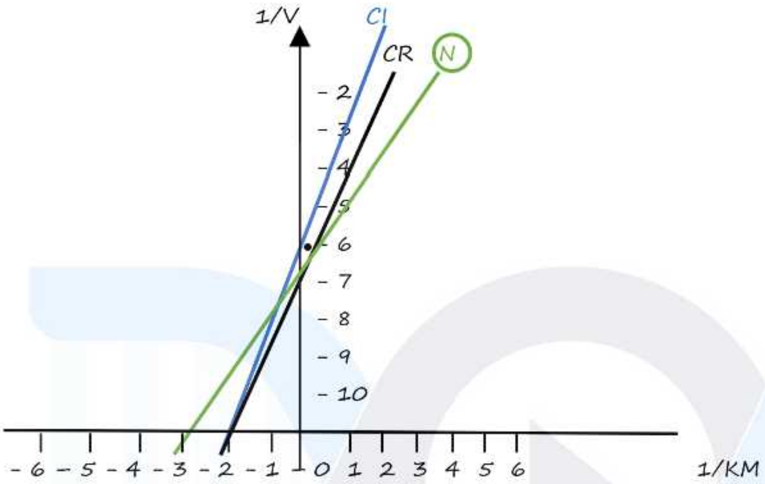
- CI RUXY
- NC SUXY
- UC LUXY
- CR RSXY – Right deviation of X axis, Same as Y axis (RSXY)



Competitive irreversible

ii. CI – RUXY

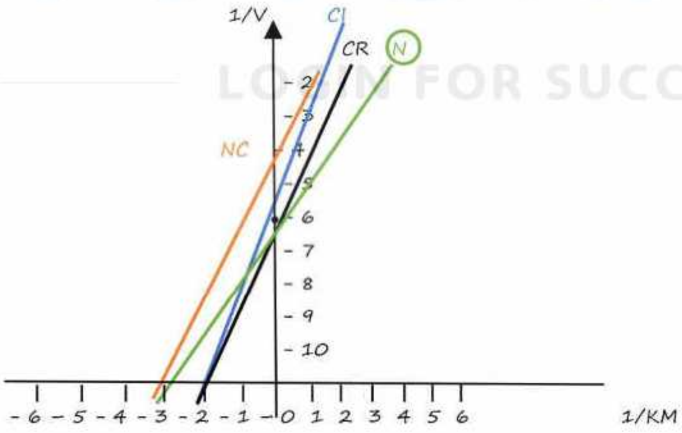
- Right deviation of X axis
- Upper deviation of Y axis



Noncompetitive inhibitors SUXY

iii. NC – Same X axis

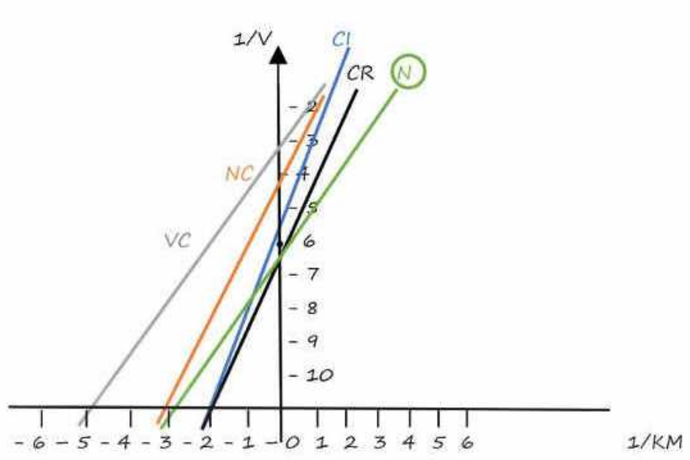
- Upper deviation of Y axis



Uncompetitive inhibitor

- UC – LUXY
- Left deviation of X axis

- Left deviation of Y axis



- As the curve moves Vmax
- As the curve moves left, KM

Summary	KM	Vmax
CR ▯ RSXY	↑	Same
CI ▯ RUXY	↑	↓
NC ▯ SUXY	Same	↓
VC ▯ LUXY	↓	↓

DOC TUTORIALS
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DRUG ACTION

Dose response curves 00:00:02

Dose response curves (DRC)

- Quantal DRC
  - All or none phenomenon
  - Eg: vomiting in animals
    - ED 50
      - Dose at which vomiting which reduced in 50% of animals
      - Effective dose
    - LD 50
      - Dose at which 50% animals are killed
      - Lethal dose
- Graded DRC
  - Potency amount of drug for response
  - Efficacy maximum effect which is produced
  - Slope
  - – Potency is considered for **dose of the drug**
  - – Efficacy is considered to select drug of choice (Efficacy highest response achieved from a drug irrespective of dose)

In humans, lethal doses cannot be calculated.
Hence, ED50 & TD50 are calculated.
ED50 is the measure od potency of drug

$$\text{Therapeutic index} = \frac{LD_{50}/\ TD_{50}}{ED_{50}} = \text{Safety \& variation in sensitivity}$$

- Drug A 1st drug
- Drug B 2nd drug

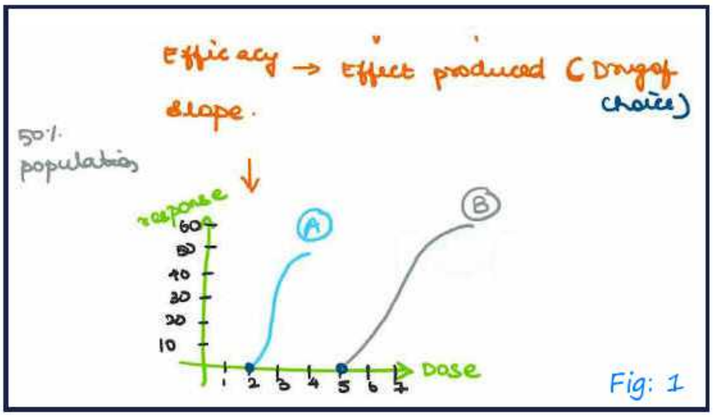


Fig: 1

- **POTENCY**: A > B (left deviation of the curve)
- **EFFICACY**: B > A (upper deviation of the curve)
- Slope of the graph – flat curves are safer than steep curves

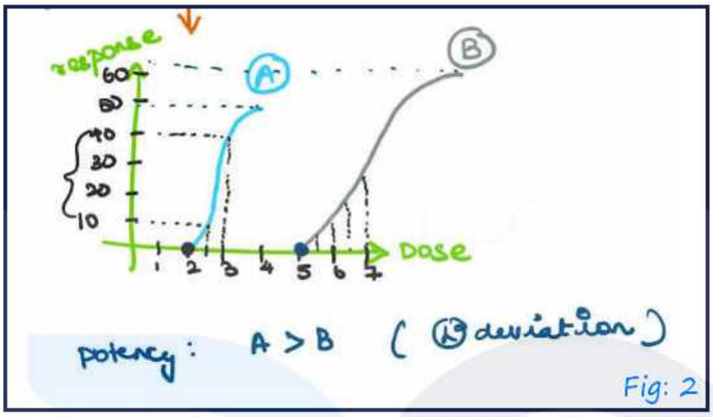


Fig: 2

  - Flat curve is safer than steep curve
- Both the Quantal & Graded DRC precisely explain the usage and sensitivity of the drug.

DRC is –

- 'U' shaped for vitamins
- Inverted 'U' shaped for Fulvestrant
- Hockey stick shaped for NAPBQI (N-acetyl para-benzo Quinone-imine) [Highly reactive minor metabolite of paracetamol]

Competitive reversible inhibitors

- (Minor highly reactive me tab of paracetamol)

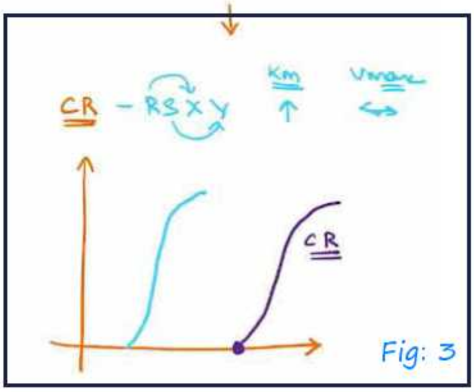


Fig: 3

- RSXY (Right deviation of X axis & same Y axis)
- K_m Increases
- V_{max} remains same

Noncompetitive inhibitors

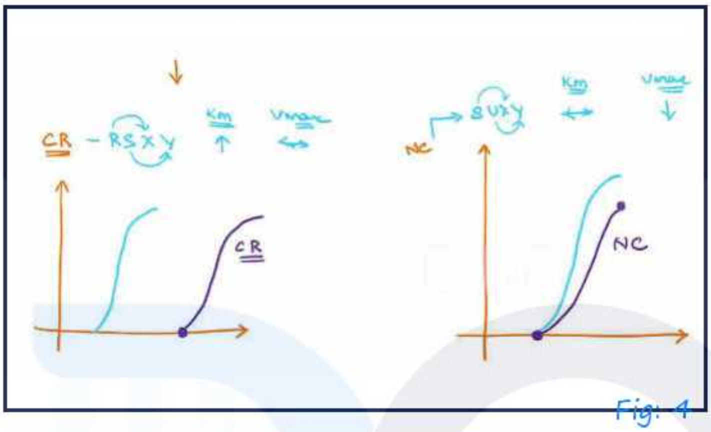
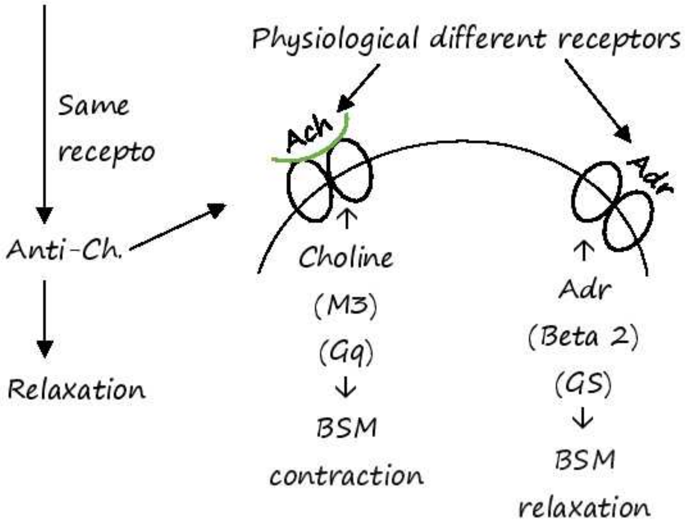


Fig: 4

- SUXY (Same X axis & upper deviation of Y axis)
- K_m remains same
- V_{max} decreases

Types of antagonism 00:13:48

- Physical e.g.: Charcoal Adsorption of drugs & utilized in treatment of poisoning
- Chemical e. g: Antacids
  - Sugammadex (chemical antagonist of Rocuronium)
  - Protamine sulfate (chemical antagonist of heparin)
- Physiological two opposite responses on two different receptors by two different neurotransmitters
- Pharmacological

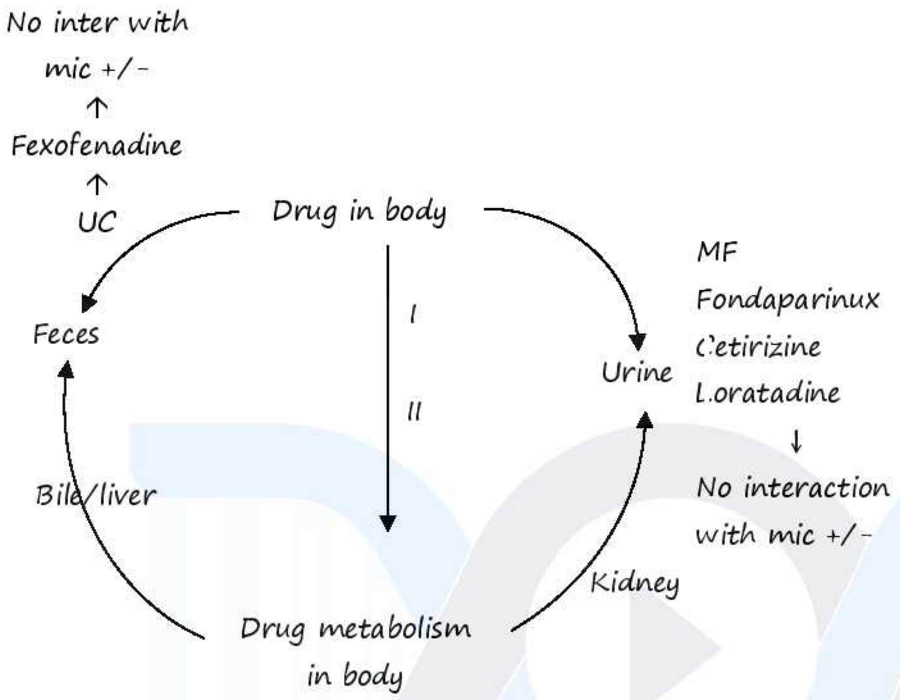

Physiological different receptors
Same
recepto
Anti-Ch.
Relaxation
Ach
Adr
Choline
(M3)
(Gq)
BSM
contraction
Adr
(Beta 2)
(GS)
BSM
relaxation

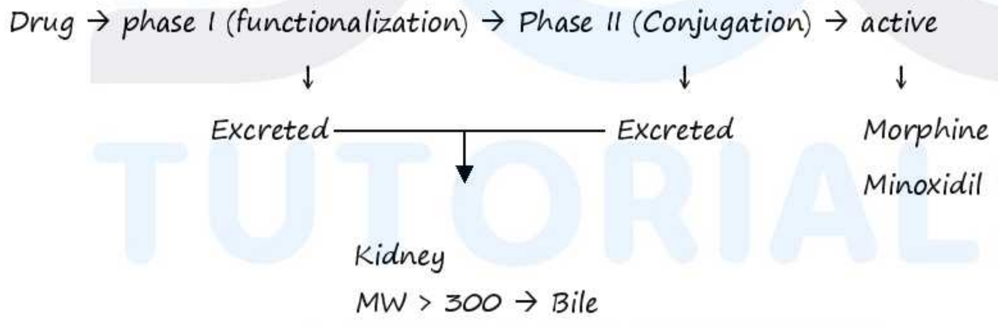
Combination of drugs 00:18:42

- **Addition → 1+1=2**
- **Synergism → 1+1=3**
  - *E. g: cotrimoxazole (cidal agent)*
  - *Trim – Trimethoprim (static agent)*
  - *Oxazole – sulfamethoxazole (static agent)*
  - *Streptogramins*
  - *Dalfopristin (static) + Quinupristin (static) = Cidal agent*
- **Potentiation 1+0=2**
  - *E. g: Levodopa + Carbidopa more CNS availability of Levodopa*
  - *Cobicistat in HAART Half-life of HAART Drugs are increased (CYP3A inhibitor)*

DRUG METABOLISM

Metabolism


No inter with
mic +/-
Fexofenadine
UC
Drug in body
Feces
I
II
Urine
MF
Fondaparinux
Cetirizine
Loratadine
No interaction
with mic +/-
Bile/liver
Kidney
Drug metabolism
in body


Drug → phase I (functionalization) → Phase II (Conjugation) → active
Excreted
Excreted
Morphine
Minoxidil
Kidney
MW > 300 → Bile

Hoffman elimination → atracurium → non → enzymatic degradation

↓

Safe in renal / liver failure.

Phase I 00:11:06

Functionalization / non – synthetic.

↓

- Oxidation → most common (MFO)
- Reduction
- Hydrolysis
- Cyclization
- DE cyclization

- Microsomal

↓

1.cyp enzymes

2.flavin mono oxygenase.

Non microsomal

↓

Cytoplasm/mitochondria

↓

1.Epoxide hydratase

2.Esterase

3.Peptidase

4.Alcohol/aldehyde dehydrogenase

5.Amidase

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TUTORIALS
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CYP 450 00:15:15

↓

- Metabolism of xenobiotics
- Synthesize of steroids and PA signaling molecules.
- Bile acid production from cholesterol

CYP 3A 4 > 2D6 > 2C19

CYP ↓ Root ward

3 ↓ family

A ↓ Sub family

4 > 2D6 > 2C19 ↓ Gene member

i. Inducers

Mnemonic:

PC GRABS TWO

CIGARETTES

↓

- Phenytoin
- Carbamazepine
- Griseofulvin
- Rifampicin
- Alcohol
- Barbiturates,
- Barbecued meat,
- John's wort
- Troglitazone
- Omeprazole
- Cigarettes

1.Acute → inhibitors
Chronic → inducer
2.BA: women > men
FPM: Men> women

ii. Inhibitors

Mnemonic:

Queen → Quinine quinidine

PC mixes vodga with ice

PC → Protease ⊖

PC → Cimetidine, chloramphenicol

- M – Macrolides
- V – valproate
- O – omeprazole

- DEC
- Grapefruit
- A – azoles
- I – isoniazid

Omeprazole
+ inducer – 1A
- inhibitor – 2c

Clopidogrel $\xrightarrow{2C19}$ Active form
(Pro drug)

Ⓐ
↓
Ⓑ

Ⓑ → Mic
⊕
↓
Increase metabolism
↓
Decrease effect of A
↓
Increase dose of A
↓
Tolerance to A
↓

B → Mic
⊖
↓
Decrease metabolism
↓
Increase effect of A
↓
Toxicity of A

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- Drug interaction
- Disease → AED

↓
+ Enzymes
↓
Increase vitamin D breakdown
↓
Vitamin D deficiency
↓

  - osteomalacia
  - # Of demineralized bone.

- Tolerance
- Drug toxicity – paracetamol.

/mic ⊕ ↓ cup

NAPBQI – N– Acetyl Para Benzo quinone imine

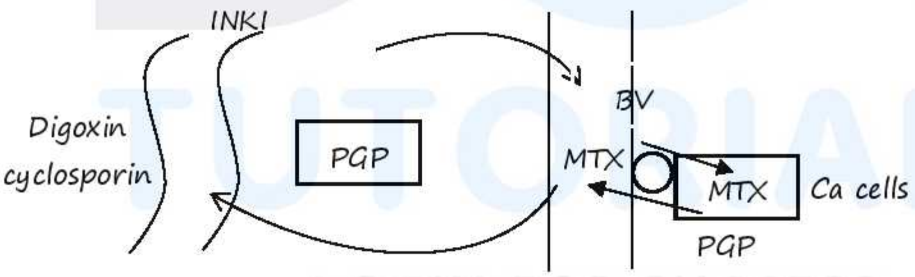
Glutathione hepatotoxicity

- Verapamil → - PGP → Increases cytotoxicity of MTR.
- P.GP → + → Rif, barbiturates

  - → ketoconazole, macrolides, quinidine

↓

Increase absorption of D/C


INKI
Digoxin
cyclosporin
PGP
BV
MTX
MTX
Ca cells
PGP

DOC TUTORIALS
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- 3A4 CSI – PA (Mnemonic)
  - CCB
  - Statins
  - Immunosuppressants
  - PI (Nevir)
  - Amiodarone
- 2D6 : A B D Villiers

- Anti – arrhythmic
- B – blocks
- Depression

– 2C19 "Ome" and "opi"

Omeprazole

clopidogrel

Phase III 00:41:07

Conjugation /synthetic reactions

i. Glucuronidation: most common

- Only phase II → +/– – chloramphenicol
- Enterohepatic circulation (esp.: ocp)
- Drug gets conjugated with glucuronide

E.g.:

i. Sulinadac

ii. PETN

iii. Ethinyl estradiol (OCP)

↓

Bile

↓

Intestine (small)

↓

Intestine (Large)

↓

Drugs separated from glucuronide

↓

Drug gets absorbed

ii. Acetylation

Preview: SHIP DC

S – Sulfonamides

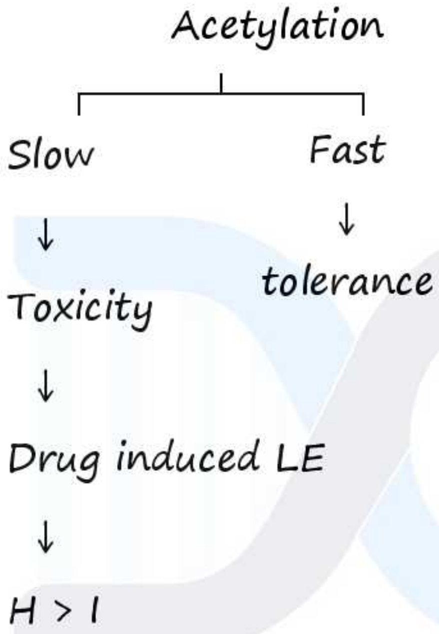
H – Hydralazine

I – Isoniazid

P – Procainamide

D – Dapsone

C – Clonazepam


Acetylation
Slow
Fast
Toxicity
tolerance
Drug induced LE
H > I

iii. Glutathione conjugation

- Para
- Nitrates

iv. Methylation

v. Sulfation

EXCRETION

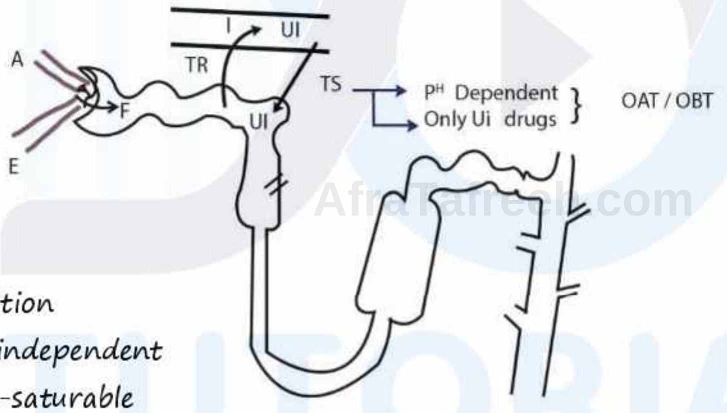
Excretion 00:00:05

Hit and run drugs

Mnemonic: MGR PA

- M – MAO $\ominus$
- G – Guanethidine
- R – Reserpine
- P – PPI
- A – Aspirin

NC/IR $\ominus$


A
E
F
I
UI
TR
UI
TS
PH Dependent
Only Ui drugs
OAT / OBT

Filtration
- PH independent
- non-saturable
- free drugs ✓
- bound drugs ☒
- both I/UI ✓

$\boxed{Vo}$ $\boxed{C_u}$

$$\boxed{Cl = \frac{cu \times vu}{cp}}$$

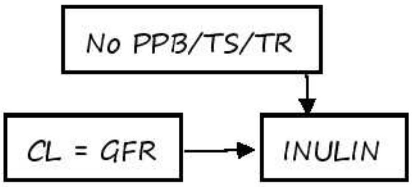
CL = [FF × GFR] + TS − TR

What if?

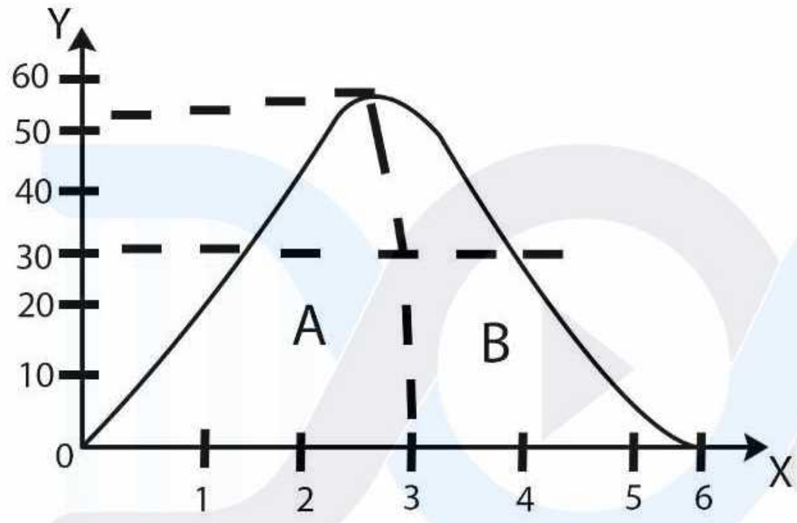
$\boxed{\text{No TS/TR}}$

CL = (FF X GFR)

What if?


No PPB/TS/TR
CL = GFR
INULIN

T ½:



T ½ → 2^0 Parameter

→0.693/k

$\boxed{K = Cl/Vd}$

$$\boxed{T_{1/2} = \frac{0.693 \times Vd}{Cl}}$$

↓

$\boxed{T_{1/2} \propto 1/cl}$

Zero		First	
↓		↓	
Constant amount/time		Constant fraction/time	
(or)		(or)	
Consent		proportion	
↓		↓	
Example: 2mg/1 hour		Example: 50%/1hour.	
↓		↓	
CP	time	CP	time
10mg	0^{th}	10mg	0^{th}
8 mg	1	5mg	1
6 mg	2	2.5mg	2
4mg	3	1.25mg	3
2mg	4	0.626mg	4
0	5	0.3125mg	5
↓		↓	
1.ROE α $(CP)^{order}$		1.ROE α $(CP)^{order}$	
↓		↓↓	
Constant		α Cp.	
2.T ½ α cp		2.T ½ → constant	
3.CL. α 1/cp		3.CL. → constant	
↓		↓	
"zero watt power"		FCT – CONSTANT	
W – war farin			
A – alcohol, aspirin		Fraction clearance T ½	
T – tolbutamide		ROE α Cp	
T – theophylline.			

DOI TUTORIALS
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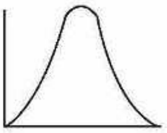
Power → phenytoin

(Saturation kinetics)

(Ist → o order)



Also michaelis – menten

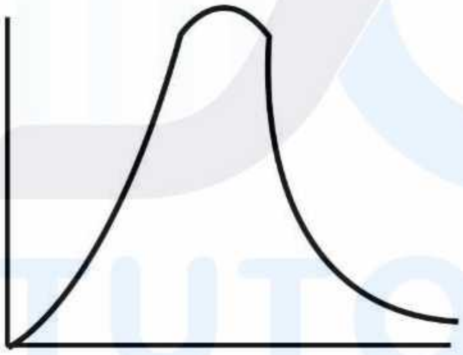
Capacity – limited

Non – linear

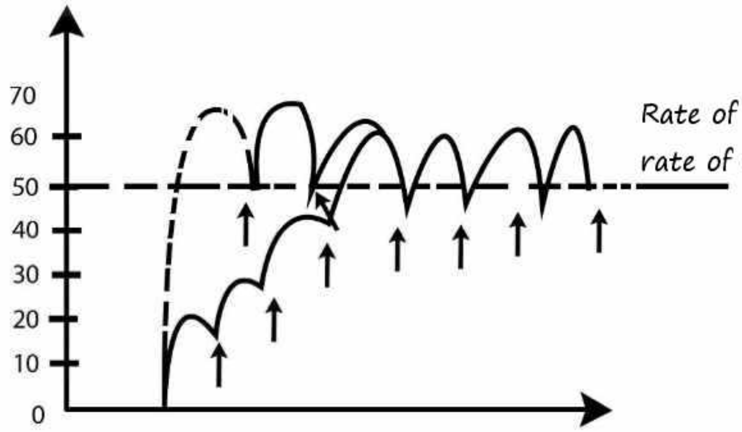
FCT → CONSTANT

↓ ROE α Cp

Majority



C^{SS} – Steady state 00:35:34



Rate of absorption = rate of excretion

$$\text{Loading Dose} = \frac{co \times vd}{F\ (P.O)}$$

$$\text{Maintenance Dose} = \frac{d \times C^{ss} \times t\,½}{f\ (P.o)}$$

CLINICAL TRIALS

Clinical Trials 00:00:10

i. Drug discovery

ii. Pre-clinical studies

iii. Investigational New Drug (IND) forms

iv. Exploratory new drug study (IND)

v. Phase I, II, III

vi. New Drug Application (NDA)

vii. Phase IV, V

Drug Discovery 00:01:28

- Target Identification
- Target Validation
- Lead Identification
- Lead Optimisation

Pre-Clinical Studies 00:01:28

- In Vitro study: e.g.: Langendorff's Heart preparation
- In Vivo: e.g.: Transgenic animals
- Ex-Vivo: Performed in vivo and analysed in vitro
- Toxicity studies: Acute, Sub acute and Chronic studies

↓

i. **Ames Test**:

- Salmonella typhimurium
- Detects mutations in bacterial DNA

Example: chloroquine (P.O) ⟶ LD → 10mg/kg
MD → 5mg/kg.

Example: Remdesivir (I.V) ⟶ LD → 200mg
MD → 100mg

ii. **Dominant lethal test**:

- Adult male is treated with a chemical before mating
- Foetal abnormalities / deaths in adult females
- Test for mutagenicity

Investigational New Drug form (IND) 00:07:00

- Investigator
- Emergency
- Treatment

Exploratory IND 00:07:40

- Phase 0 clinical trials: Micro dosing study
    - 1/100th of the human dose
    - Upto max of 100micro grams
    - Healthy volunteeers (<10) are involved
    - Only pharmacokinetic study
    - To be sure of mechanism of action of drug

Phase I: 00:09:00

- Healthy volunteers are involved (except for anti-cancer therapy)
- Ph. Actions
- Open label study
- Maximum tolerable dose is calculated

Phase II: 00:10:09

- It is the first in-patient study
- Single blind study
- Therapeutic Exploratory study
- Small scale trial
- Efficacy & Safety

Phase III: 00:11:05

- Therapeutic confirmatory study. First heterogeneous population study
- Double blind study
- Multi centric
- Comparison with established treatment

After Phase III

↓

NDA (new drug application) is submitted

↓

Market

(drug will come into market after approval by competent authorities)

Phase IV: 00:12:50

- Understanding the Rare / Long term adverse drug reactions
- Post Marketing surveillance
- No need for ethics committee clearance

Phase V: 00:13:30

- Pharmaco-Epidemiology

Key points on these clinical trials 00:14:32

i. Placebo → Not used in Phase I & II (used especially in phase III)

ii. Blinding & Randomisation → used only in Phase II and III (no such thing in I & IV)

iii. Ethics committee clearance → is necessary for Phase I, II and III

ANS BASICS

1. Acetylcholine – Autonomic Nervous System, behaves as an autacoid on two areas –
   a. Placenta
   b. Ciliary epithelial cells
2. Hypoglycemia warning symptoms – masked, when patient receives hypoglycemia drug with a β-blocker, except sweating
3. Acetylcholine esterase inhibitors – metabolism inhibitors
   Adrenaline/NA – reuptake inhibitors
4. Nicotine receptor N_N present in adrenal medulla
5. Acetylcholine – inhibitory effect on heart (G_i receptor)

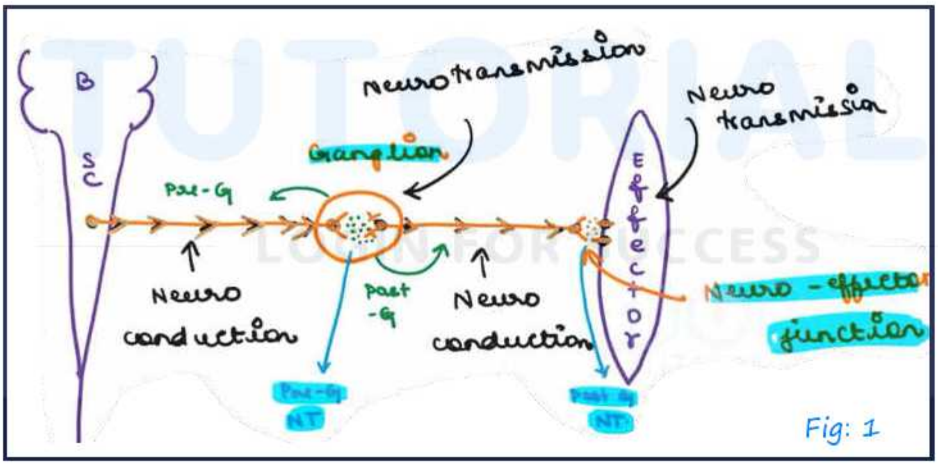
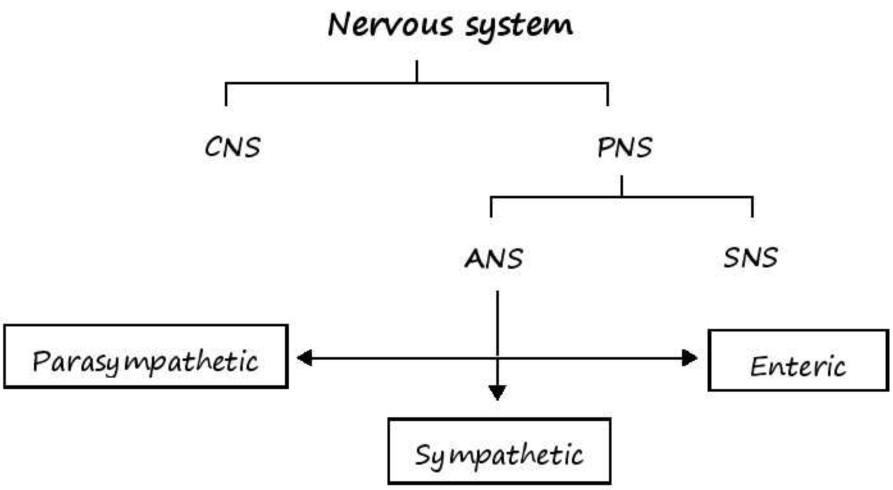

B
SC
Neurotransmission
Ganglion
Pre-G
Post -G
Neuro conduction
Neuro conduction
Neuro transmission
Effector
Neuro-effector junction
Pre-G NT
Post-G NT

Fig: 1


Nervous system
CNS
PNS
ANS
SNS
Parasympathetic
Enteric
Sympathetic

- Enteric nervous system is a semi-autonomic nervous system
- Parasympathetic Nervous System: tissue building reaction (Rest & digest response)
- Sympathetic Nervous System: Emergency Response (Fright, Fight, Flight response)
- Noradrenaline – Neuro-transmitter in all the areas except thermoregulatory sweat glands where Ach is the neuro-transmitter
- Modified sympathetic ganglion is called adrenal medulla

DOC TUTORIALS
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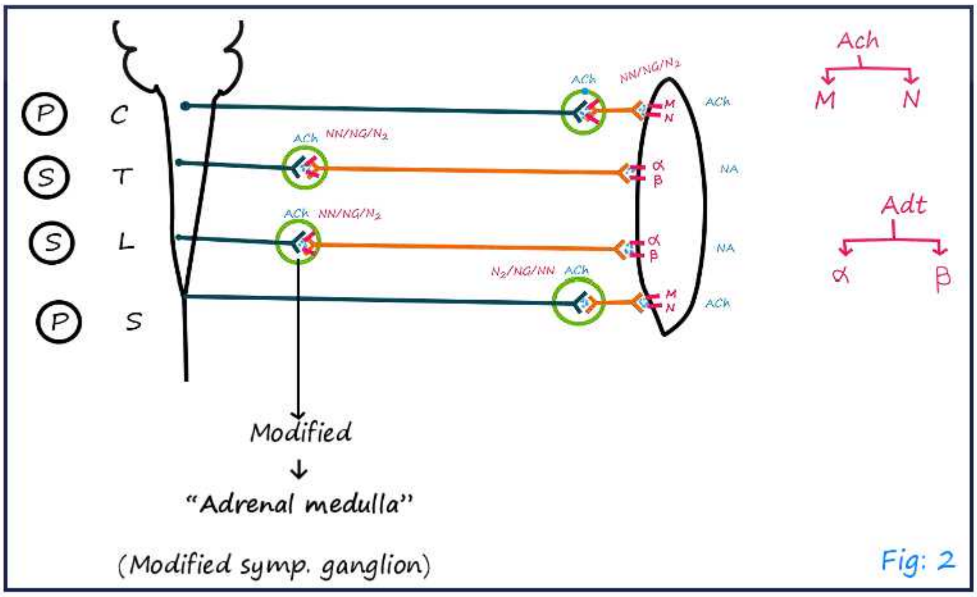

P
S
S
P
C
T
L
S
ACh
NN/NG/N₂
M
N
ACh
ACh
NN/NG/N₂
α
β
NA
ACh
NN/NG/N₂
α
β
NA
N₂/NG/NN
ACh
M
N
ACh
Ach
M
N
Adt
α
β
Modified
"Adrenal medulla"
(Modified symp. ganglion)

Fig: 2

Parasympathetic	Sympathetic
Tissue building	Emergency response
Pre-ganglionic: ACh Post-ganglionic: ACh	Pre-ganglionic: Ach Post-ganglionic: NA, Adr, Dopamine, 5-HT
Cholinergic Nervous System	Adrenergic Nervous System
Craniosacral part of spinal cord	Thoraco-lumbar part of spinal cord
Miosis	Mydriasis
Supplies ciliary muscle	No supply to ciliary muscle

C's of parasympathetic nervous system 00:20:04

- Cholinergic Nervous System
- Craniosacral – arises from this part of spinal cord
- Constriction of Pupils – miosis
- Ciliary muscle supply – helps in accommodation

Cholinergic system

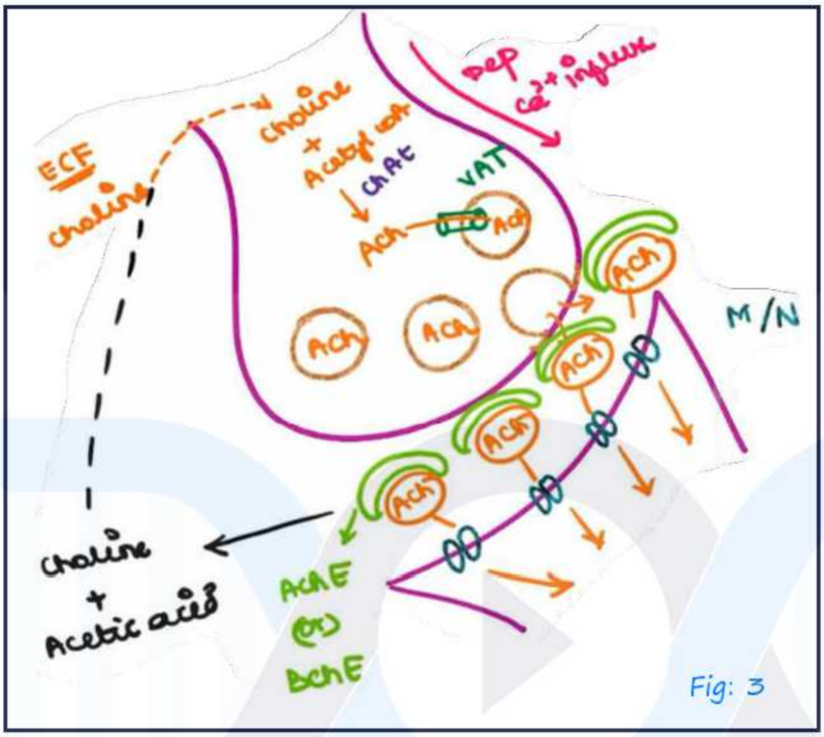

ECF
choline
Choline
+
Acetyl CoA
ChAt
ACh
VAT
ACh
Dep
Ca^{2+} influx
ACh
ACh
ACh
ACh
ACh
ACh
ACh
M/N
Choline
+
Acetic acid
AChE
(or)
BchE

Fig: 3

- **Rate limiting step** – Choline transfer from ECF into the cell
- ChAt enzyme – Choline Acetyl Transferase
- VAT – Vesicle associated transporter (Acetylcholine transport into vesicle)
- Impulse from brain → depolarization of neuron → Ca^{2+} release → vesicle fusion with presynaptic terminal
- Acetylcholine Esterase/Butyryl choline esterase – breaks ACh into Choline + Acetic acid
- Primary mechanism of termination of action of ACh **is metabolism**

Dopaminergic system 00:38:30

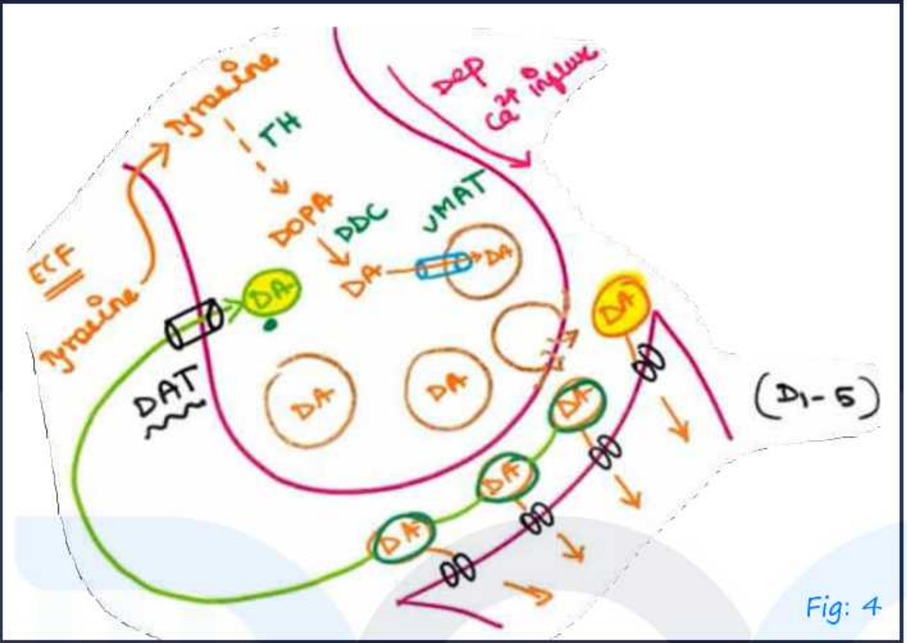

ECF
Tyrosine
Tyrosine
TH
DOPA
DDC
DA
VMAT
DA
Dep
Ca^{2+} influx
DAT
DA
(D1-5)

Fig: 4

- Tyrosine from ECF taken up
- **Rate limiting step**: Tyrosine $\xrightarrow[\text{Hydroxylase}]{\text{Tyrosine}}$ DOPA
- DDC – Dopamine Decarboxylase
- **Transporter of Dopamine into vesicles** – Vesicular Monoamine Transporter
- **Depolarization → Calcium influx → exocytosis of vesicles → Dopamine release**
- **Dopamine receptors** – D_1, D_2, D_3, D_4, D_5
- DAT: Dopamine Transporter – *helps in reuptake of* Dopamine from synapse
- Termination of Action mechanism – **reuptake (presynaptic, extra-neuronal) & diffusion**
- **Metabolism by enzymes:** Catechol O-Methyl transferase (COMT) & Monoamine oxidase (MOA)

- **COMT Location** – Adrenal medulla, liver, kidney, tumors of Chromaffin tissue
- **MOA Location** – liver, kidney, intestinal mucosa, sympathetic presynaptic neurons
- Sympathetic nerves ONLY Monoamine Oxidase enzyme present
- Synthetic Non-catecholamines: Resistant to enzymatic degradation
- **Dopaminergic neurons** – hydroxylation, decarboxylation

Noradrenergic system

- Inside vesicles – Dopamine → Noradrenaline + ATP + Chromogranin
- **Co-transporters** – Vesicles which is stored up with primary transporter (ATP, Chromogranin)
- **Noradrenergic neurons** – hydroxylation, decarboxylation, inside vesicles hydroxylation

Adrenergic system

- Inside vesicles – Dopamine $\xrightarrow{\text{Dopamine } \beta\text{-hydroxylase}}$ Noradrenaline
- Noradrenaline $\xrightarrow[\text{SAM}]{\text{PNMT}}$ Adrenaline
  - SAM – S-adenosyl Methionine
  - PNMT – Phenyl Ethanolamine N-methyl Transferase

- Receptors – α & β
- Reuptake – Epinephrine transporter

Drugs affecting neurohumoral transmission

- Drugs inhibiting rate-limiting step (**HE ME**)
  - Cholinergic – Hemicholinium (choline uptake)
  - Adrenergic – Metyrosine (tyrosine hydroxylase)
- Drugs inhibiting vesicular transport (**VES & RES**)
  - Cholinergic: Vesamichol (VAT)
  - Adrenergic: Reserpine (VMAT)
- Drugs inhibiting release (**BOGUAN**)
  - Cholinergic: Botulinum toxin (blocks release of ACh)
  - Adrenergic: Guanethidine (blocks release of Adr & NA)
- **NOTE**: Black widow spider toxin increases release of ACh. (Opposite effect of Botulinum toxin)
- Ganglion Blockers
  - Hexamethonium
  - Trimethaptan
- Monoamine Oxidase inhibitors
  - Tranylcypromine
  - Moclobemide
- Monoamine Oxidase B inhibitors
  - Selegiline
  - Rasagiline

- Catechyl O-methyl transferase inhibitors
  - Entacapone
  - Tolcapone
- Reuptake inhibitors
  - Cocaine
  - TCA
  - Reboxetine (Norepinephrine Selective Reuptake Inhibitor NSRI)

Receptors

Cholinergic Receptors
- MUSCARINIC – G Protein Coupled Receptors
- NICOTINIC – Ionic Channels

MUSCARINIC RECEPTORS – 5 subtypes

M_1	M_2	M_3	M_4	M_5
G_q	G_i	G_q	G_i	G_q

M_1 - G_q – enterochromaffin like cells – increases gastric acid secretion

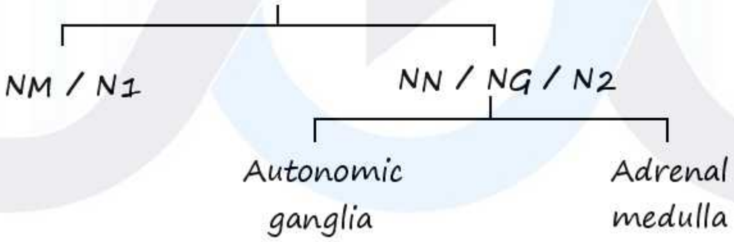
M_2 - G_i – presynaptic and atrial heart muscles (increases heart rate, increases AV conduction)

M_3 – G_q – ↑ exocrine gland secretion, ↑ gut motility, miosis, accommodation, bronchoconstriction, bladder constriction

M_4 – G_i –
M_5 – G_q –] CNS – Stimulation followed by depression

- Relaxes sphincters except Lower Esophageal Sphincter
- Blood vessels – production of Nitric Oxide – vasodilation

Nicotinic receptors


NM / N1
NN / NG / N2
Autonomic ganglia
Adrenal medulla

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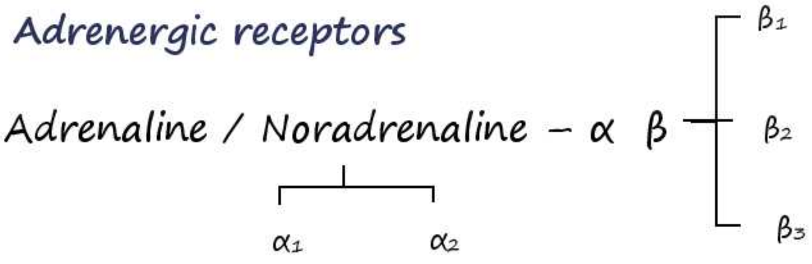
Adrenergic receptors


Adrenaline / Noradrenaline – α β
α1
α2
β1
β2
β3

Dopamine receptors – D_1, D_2, D_3, D_4, D_5

- D_1 & D_5 are similar, D_1 – like receptors
- D_2, D_3 & D_5 are similar – D_2-like receptors

Serotonin receptors – 5-HT$_{1-7}$

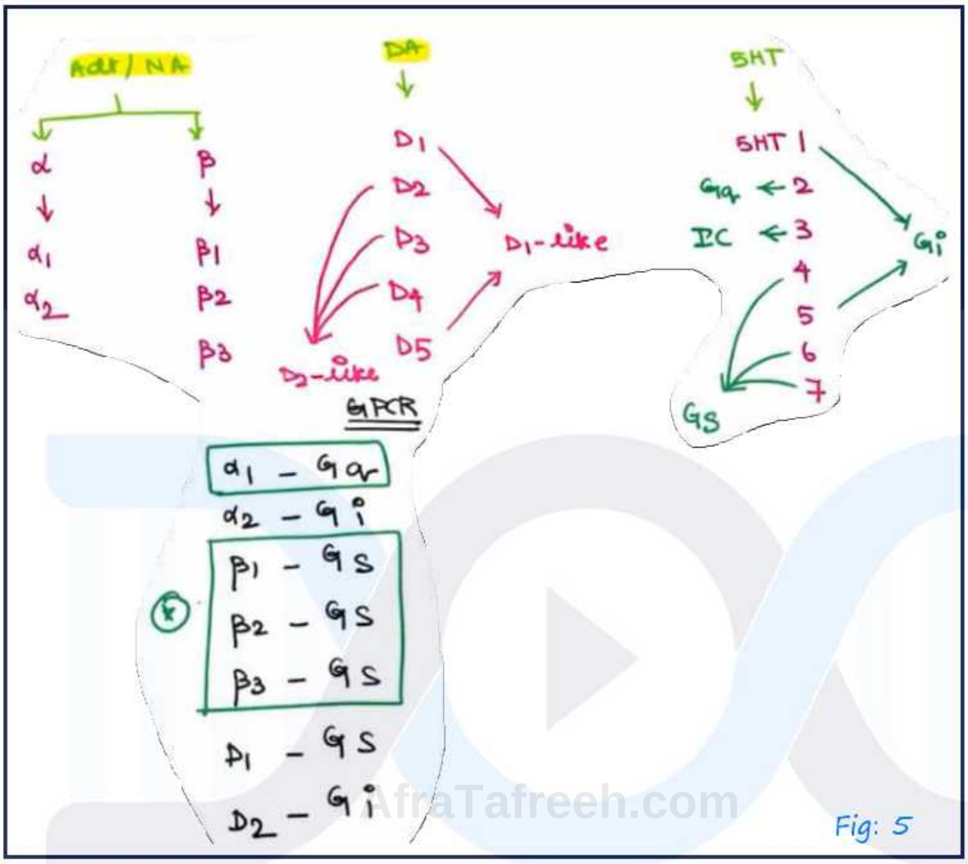

Adr / NA
α
β
α1
α2
β1
β2
β3
DA
D1
D2
D3
D4
D5
D1-like
D2-like
5HT
5HT 1
Gq ← 2
IC ← 3
4
5
6
7
Gi
Gs
GPCR
α1 – Gq
α2 – Gi
β1 – Gs
β2 – Gs
β3 – Gs
D1 – Gs
D2 – Gi

Fig: 5

α2 SUBTYPE	LOCATION
α2A	Pre-synaptic
α2B	Post-synaptic
α2C	Post-synaptic

α1 SUBTYPE	LOCATION
α_{1A}	Prostate gland
α_{1B}	Blood vessels
α_{1D}	Detrusor

β-RECEPTORS

β_1 receptors
- Heart – positive inotropic, chronotropic and dromotropic
- Kidneys – increases renin release

- β_2 – **receptors** → bronchial smooth muscle, uterus, GIT, blood vessels, bladder, pancreatic β-cells **roles**: relaxation of above-mentioned smooth muscles inhibits release of autacoids from mast cells skeletal muscles – tremors
- β_3 – **receptors** → Brown adipose tissues, produces non-shivering thermogenesis & Lipolysis

Bladder – $\beta_3 > \beta_2$ (relaxation)

β_3 agonist – MIRABEGRON – overactive bladder treatment; CYP2D6 inhibitor

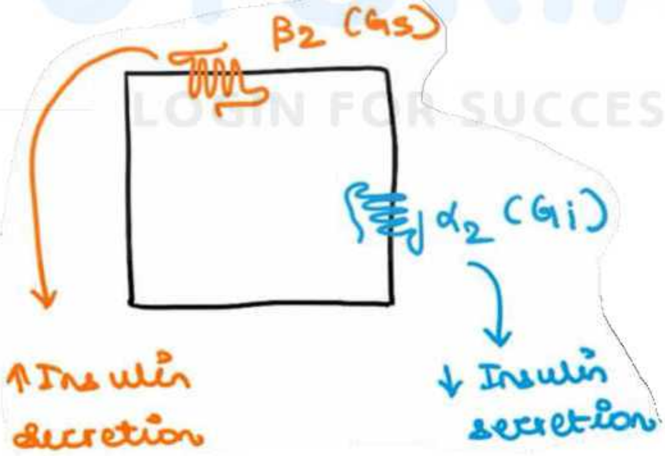
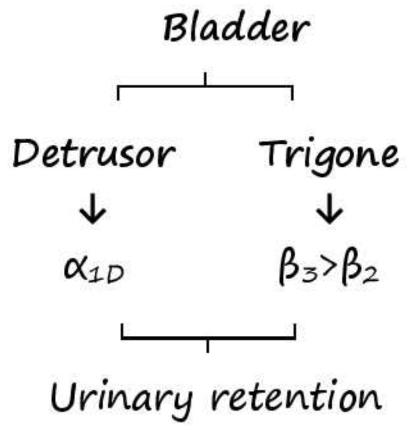
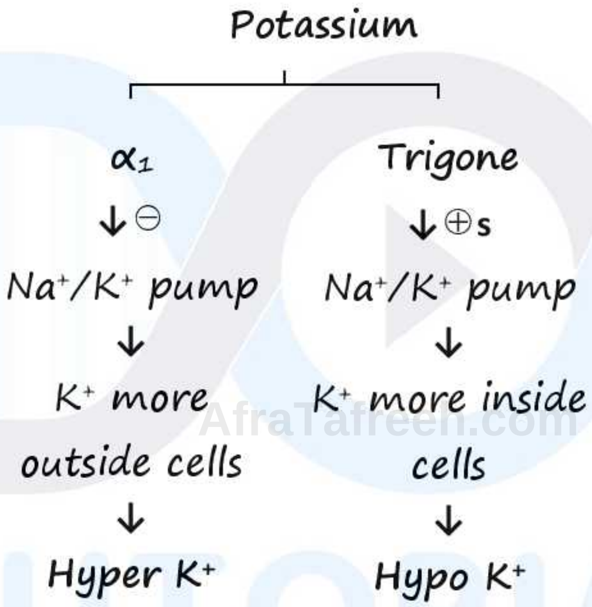


Fig: 6


Bladder
Detrusor
Trigone
α_{1D}
$\beta_3 > \beta_2$
Urinary retention


Potassium
α_1
Trigone
⊖
⊕s
Na^+/K^+ pump
Na^+/K^+ pump
K^+ more outside cells
K^+ more inside cells
Hyper K^+
Hypo K^+

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- Beta blockers causing arrhythmias
- Radial muscle of eye – Adrenergic (α_1) G_q – Mydriasis (CONTRACTION)
- Circular muscle of eye – Cholinergic (M3) Gq – Miosis (CONTRACTION)

In eyes

- There are two types of iris muscles-
  i. Circular supplied by parasympathetic system (M3) □ Gq coupled □ causes mitosis.

ii. Radial muscles supplied by sympathetic system (L1) □ Gq coupled □ causes mydriasis.

- Muscarinic agonist
  a. effect on circular muscles □ contraction □ mitosis.
  b. effect on ciliary muscle □ contraction □ accommodation.
- Muscarinic antagonist effect on circular muscles □ no contraction
- Mydriasis effect on ciliary muscles □ no contraction Cyclopegia
- Adrenergic agonist
  a. effect on radial muscle □ contraction □ mydriasis.
  b. Effect on ciliary muscle □ no effect □ no supply
- Mydriasis caused by anticholinergic agent is called passive mydriasis.
- Mydriasis due to adrenergic system is called active mydriasis because it involves contraction of radial muscles

CHOLINERGIC PHARMACOLOGY

Two types

- Directly acting – act at the muscarinic and nicotinic receptors
- Indirectly acting

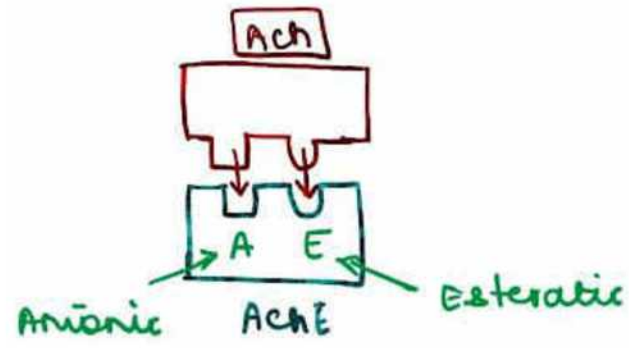
Directly acting agents 00:03:58

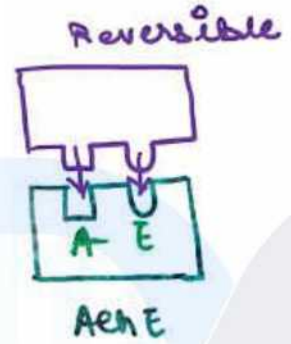
- Drugs acting directly acting on Muscarinic receptors are:
  - Methacholine (M2 selective agent with additional nicotinic action)
  - Carbachol (Maximum nicotinic activity)
  - Bethanechol (M3 activity—exocrine glands, ciliary muscles, GIT, pupillary sphincter, bladder SM, bronchial sm)
  - Pilocarpine (non-selective agent, acts at maturity of muscarinic receptors)
  - Cevimeline (new drug) (M1+ M3 receptors) (minimal effect on heart)
- Drugs acting directly on the nicotinic receptors are:
  - Nicotine
  - Succinylcholine
  - Varenicline (Partial agonist – used in smoking cessation) (maximum affinity for the receptor)

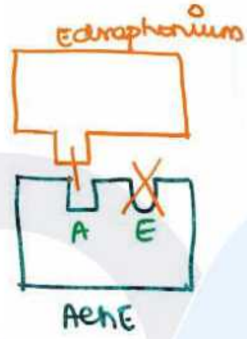
Bethanechol	Pilocarpine
Used for gastric atony following bil. vagotomy	It can be administered via ouster or via eye drops.
urinary retention post operatively	Contraindicated in hyperthyroidism as it increases the tendency of arrhythmia.
If given as IV or IM, may cause cardiac arrest As the selectivity is lost.	Used in sjogren's syndrome along with Cevimeline (m1+m3 agonist)
Slow IV infusion is preferred if given via parenteral route	

Indirectly acting agents 00:11:25

- They inhibit Acetylcholine esterase
- Acetyl choline accumulates
- The t1/2, concentration and action of AchE increases.
- The Ache can be inhibited by reversible and irreversible inhibitors.
  - i. Reversible AchE inhibitors are carbamates such as—physostigmine, neostigmine, pyridostigmine, edrophonium, Rivastigmine, Galantamine and donepezil.
    - Acridine derivatives such as tacrine (obsolete now due to dangerous hepatotoxicity)
  - ii. Irreversible AchE inhibitors are Organophosphorus compounds such as parathion, malathion, ecothiopate, tabun
    - Carbamates such as carbonyl and propoxur.
      - ENDRINE is an ORGANOCHLORIDE compound.
      - Reversible Ache inhibitors bind and inhibit Ache.
      - Ache has 2 active sites—anionic and the esteratic sites. Reversible inhibitors bind to both the sites, whereas, the irreversible inhibitors bind to a single site.


Ach
A
E
Anionic
AChE
Esteratic


Reversible
A
E
AChE


Edrophonium
A
E
AChE

- All the reversible drugs bind to both the sites except for Edrophonium
- As the edrophonium is short-acting, it is used to diagnose myasthenia gravis

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Neostigmine v/s physostigmine 00:18:29

Neostigmine	Physostigmine
Synthetic compound	Natural compound
Quaternary ammonium compound (ionized)	Tertiary ammonium compound (unionized)
Poorly absorbed through gut	Can be given orally—well absorbed through gut
Cannot cross the blood brain barrier	Crosses the blood brain barrier (just like 5FU)
Eliminated through urine	Bile dissolvable and excreted through feces
Used in myasthenia, curare poisoning, cobra bite (Along with atropine)	Used in belladonna, datura and atropine poisoning. 2mg of physostigmine is given in atropine poisoning

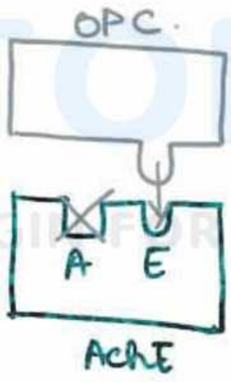
Other cholinomimetics crossing the Blood Brain Barrier

- High CNS penetration
- Ns—all nicotinic drugs except succinylcholine
- PR—all 'P' drugs except pyridostigmine
- A – Alzheimer's drugs such as Rivastigmine, galantamine, donepezil.

- Irreversible AchE inhibitors—organophosphorus compounds
- Parathion and Malathion are both prodrugs that are converted to their active forms--- paraoxon and malaoxon
- Parathion is the most commonly used drug. Methyl parathion is as known as Folidol dust or neostigmine
- Malathion has minimal toxicity as it is rapidly metabolized by the plasma carboxyl esterase enzyme and hence used topically for Pediculosis

MOA of irreversible inhibitors 00:23:20

- Bind only to the esteratic site



- Property of conversion of AchE to MIP AchE is called the AGEING complex
- Drugs like Oximes cannot be given after Ageing complex is formed. They have to be given well in advance before the complex is formed

Clinical features

- Cholinergic symptoms
- Muscarinic symptoms
- M1—enterochromaffin-like cells
- M2—heart (decreases HR)
- M3—exocrine glands (increases secretions)
- Increased gut motility, mitosis, Broncho and
- Bladder contraction (urinary voiding)
- Red tears in organophosphorus compounds poisoning as they cause accumulation of porphyrin in the tear glands
  - Nicotinic symptoms Calculations and twitching's

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Treatment of OPC poisoning

- Specific antidote—atropine and oximes
- DOC – atropine

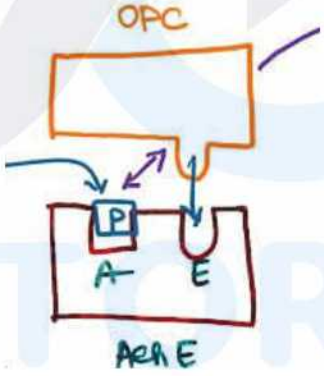
Atropine 00:26:24

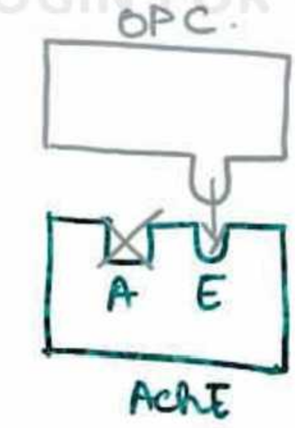
- It is an anticholinergic agent (anti muscarinic agent)
- 2mg is given in OPC poisoning IV every 10 min until signs of atropine toxicity appear
  - Advantage
    - DOC in treatment of OPC and carbamate poisoning.

- Disadvantages
  - Causes only muscarinic reversal.
- Has no nicotinic activity.
  - Blocks all muscarinic receptors (non-selective).
  - Can penetrate BBB, can antagonize central effects in OP poisoning

Oximes 00:28:20

- E.g.—pralidoxime, obidoxime, diacetyl monoxime.
- Obidoxime is more potent than pralidoxime.





- Pralidoxime need a free anionic site to act which is not in the case of carbamate poisoning. Therefore, pralidoxime is ineffective in carbamate poisoning.
- Pralidoxime forms a bond with the OPC and pulls it out of the esteratic site of AchE. It reactivates the cholinesterase enzyme by forming a phosphor-oxime complex and hence is called as cholinesterase reactivator.
- 1-2 gm IV within 30 min (to avoid the Ageing process).

Advantage

- causes both muscarinic and Nicotinic reversal
- For treating the nicotinic symptoms, we prefer oximes >> atropine
- Disadvantage—effective only in OPC poisoning. It is not used in carbamate poisoning
- Chronic OPC poisoning--
- Sensory disturbances initially followed by polyneuritis
- No specific antidote for chronic OPC poisoning

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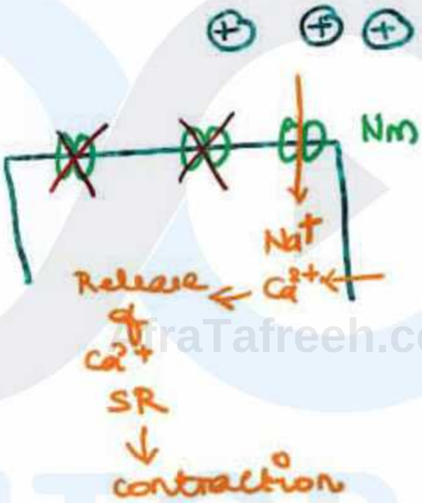
Myasthenia Gravis 00:38:38

- Autoantibodies targeting the Nm receptors at the neuromuscular junction of skeletal muscle.
- Diagnosis—edrophonium (Tensilon Test) - 2mg – wait for 45 seconds
- skeletal muscle relaxed in myasthenia gravis due to inadequate Nm receptors. Whereas, skeletal muscle relaxation in cholinergic crisis due to increased Ach and exaggerated release of calcium from the sarcoplasmic reticulum with initial fasciculation's and contractions and later loss of calcium with resultant relaxation.
- After 45 seconds—the weakness worsens in cholinergic crisis. STOP edrophonium and start on atropine
- If the weakness improves, i.e., improvement in strength unaccompanied by lingual fasciculation's—it is the positive edrophonium test for myasthenia
- Edrophonium, though reversible AchE, acts only on the Esteratic site and is short acting drug. Therefore, it is used for the diagnosis of Myasthenia
- Once it is confirmed that the patient has myasthenia, 8mg of edrophonium is administered
- Two different treatment options for myasthenia--

- Symptomatic treatment such as Neostigmine, pyridostigmine and ambenonium. (Does not alter disease progression)
- Treating the cause such as Azathioprine, cyclosporine and prednisolone (will alter disease progression)

Drugs that exacerbate Myasthenia 00:45:12



- The Nm receptors at the neuromuscular junction allow the influx of Na+ and Ca+ which turn releases more calcium from the sarcoplasmic reticulum (calcium induced calcium release).
- The calcium now causes the muscle to contract.
- Drugs that because myasthenia have a charge on them but are bigger molecules and hence are stuck at the receptors

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- since there is block at the receptors, there is exacerbation of skeletal muscle relaxation and hence myasthenia worsens.
- Any drug that is a single charged molecule exacerbates myasthenia.
- Mnemonic for the drugs: "Amitabs MCQ remember beta has BP"
- Aminoglycosides
- Macrolides, magnesium
- Curare drugs, caine and colistin drugs
- Quinidine, quinine and quinolone
- Beta blockers
- Botulinum toxins
- Penicillamine

Anticholinergics

Tertiary ammonium compounds (unionized)	Quaternary ammonium compounds (ionized)
↓	↓
Atropine Homatropine Tropicamide Scopolamine	Ipratropium bromide Tiotropium bromide clidinium
↓	↓
Fat soluble & highly penetrable as they are Unionized	As they are ionized → water soluble & less penetrable
↓	↓
(Central activity: Local activity) is higher	Central: Local is lower Activity
↓	↓
In poisoning physostigmine can be used	In poisoning, neostigmine is used

- Action of Anticholinergics on eye → Cyclopentolate (Short acting) & Tropicamide (Short acting) → Used
- In refractory measurements & ophthalmoscopic examination
- Long-acting anticholinergics → Atropine & Homatropine → Adjunct to phenylephrine to prevent synechiae (in anterior uveitis)

- Atropine is preferred for refractory measurements in children as they have strong ciliary tone. (Strong cycloplegic agent)

Alpha Agonists on eye

- Phenylephrine → Fundoscopic examinations without cycloplegia

Vesicoselective Agents 01:07:50

i. Oxybutynin → Increases bladder holding capacity
ii. Trospium
iii. Darifenacin
iv. Solifenacin
v. Tolterodine
vi. Fesoterodine

- Anticholinergic with local anesthetic property → Flaboxate which is used in bladder stones
- Propantheline → Delays gastric emptying
- Drug induced Parkinson's → Benzhexol

Atropine 00:56:02

- Competitive, reversible, non-selective, muscarinic antagonist
  - No action on nicotinic receptors

- All secretions decrease as it is a non-selective muscarinic antagonist (except breast milk)
- The decrease in secretions is the primary cause of hyperthermia
- Retention if urine
- Though anti-cholinergic, decreases gastric motility is not seen in atropine as there are many other compensatory mechanisms (5HT, encephalin)
- However, weak decreases in GI motility is seen
- Increase in the heart rate is not seen initially on parenteral administration of atropine. Initial transient bradycardia is a accompanied by tachycardia
- D.O.C for OPC poisons carbamates poisoning early
- Long-acting drug (not preferred for ophthalmic use)

ADRENERGIC DRUGS

- There are alpha1, alpha 2, beta1, beta2, beta3, D1, and D2 receptors.
- These are G protein coupled receptors.

Drug and receptors

i. Adrenaline

  - It acts on all the receptors and produces action.
  - We don't take alpha 2 into consideration because it is a GI coupled receptor. It has a special property called internalization.

ii. Noradrenaline

  - It has no beta2 action.
  - alpha 1 receptor causes vasoconstriction. beta2 receptor causes vasodilatation. Since there is no beta2 action, noradrenaline only acts on alpha 1 receptor and causes vasoconstriction only.

iii. Isoproterenol

  - It has only beta action and causes vasodilatation.

Receptor and drug

- alpha 1 receptor – Adrenaline has equal action to Noradrenaline which is far greater than Isoproterenol.
- Beta 1 receptor – Isoproterenol has greater action than Adrenaline which is equal to Noradrenaline.

- beta2 receptor - Isoproterenol has equal action to adrenaline which is far greater than noradrenaline.

Selective agnostic agents

- Alpha 1 receptor stimulation - Increase in BP due to vasoconstriction, followed by reflex bradycardia.
- Beta 1 receptor stimulation - Increase in pulse pressure, stroke volume, cardiac output, and blood pressure.
- Beta 2 receptor stimulation - Decrease in BP due to vasodilatation, followed by reflex tachycardia.

Mixed agnostic agents 00:11:25

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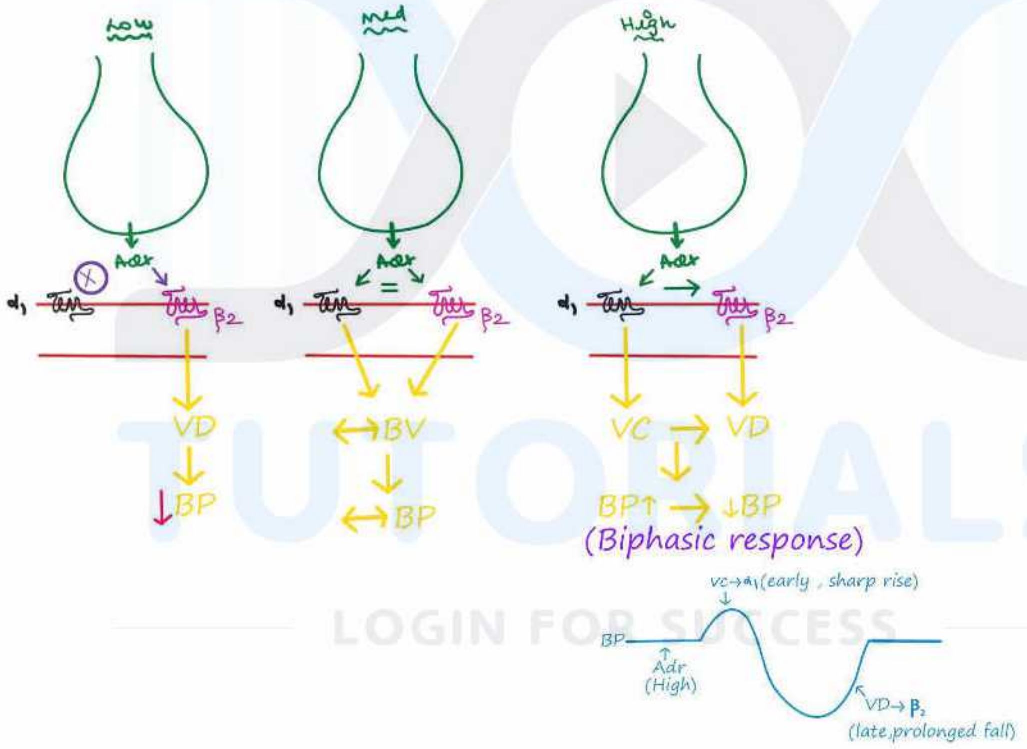
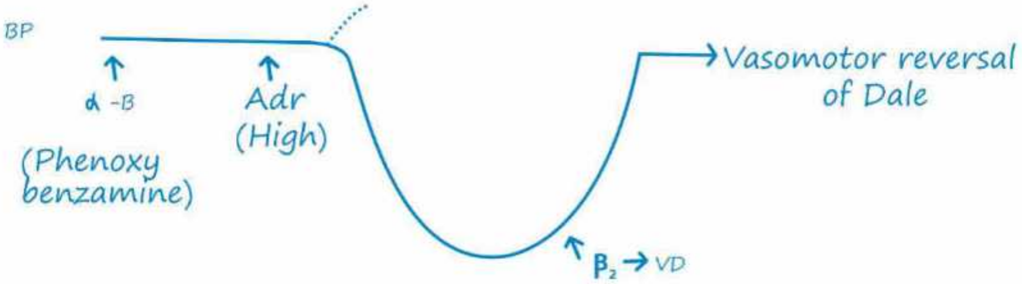
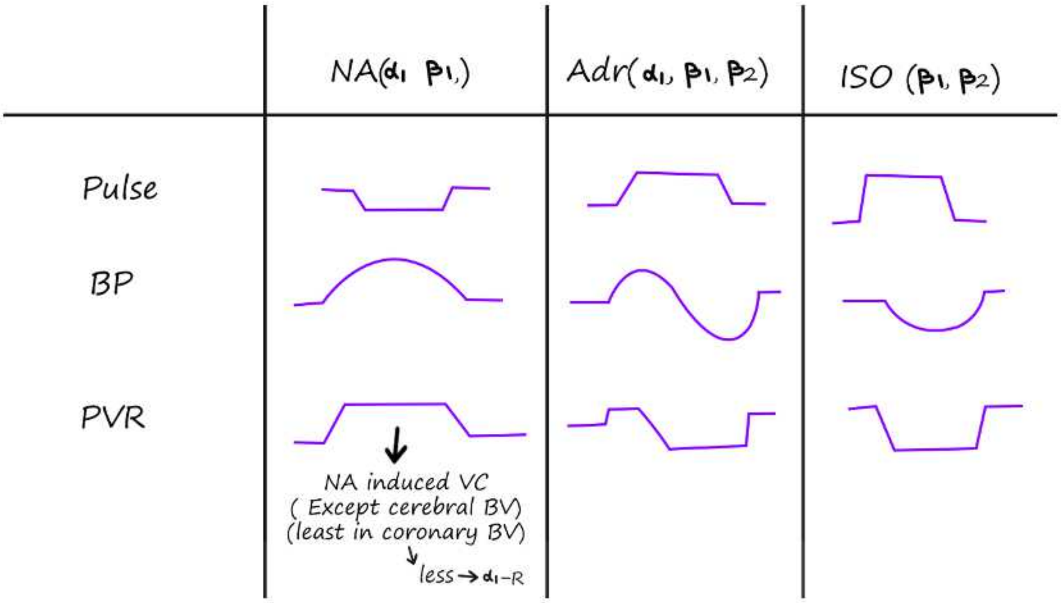
- Noradrenaline has action only on alpha 1 and beta 1 receptors. No action on beta 2.
- Due to Alpha 1 - there is increase in blood pressure followed by decrease in heart rate.
- Due to Beta 1 - there is increase in pulse pressure, stroke volume, cardiac output, blood pressure, and heart rate.
- If noradrenaline is administered together - BP is increased, stroke volume is increased, stroke volume is increased, pulse pressure is increased, whereas heart rate is initially increased followed by decrease.
- In isolated heart preparation - Heart rate increases and there is no decrease due to no reflex mechanism.

Adrenaline 00:14:30

- It has three different doses.
- As dose increases, alpha 1 selectivity increases.
- Low dose - Beta 1 + Beta 2 activity
- Medium dose - Beta 1 + (Alpha 1 = Beta 2)
- High dose - Beta 1 + Alpha 1 occurs first followed by Beta 2. Hence biphasic response.


Low
Med
High
Adr
Adr
Adr
α1
β2
α1
β2
α1
β2
VD
↓BP
↔BV
↔BP
VC → VD
BP↑ → ↓BP
(Biphasic response)
VC→α1 (early, sharp rise)
BP
Adr (High)
VD→β2 (late prolonged fall)




NA(α1, β1)
Adr(α1, β1, β2)
ISO (β1, β2)
Pulse
BP
PVR
NA induced VC
(Except cerebral BV)
(least in coronary BV)
less → α1-R

Biphasic response in blood pressure

- Adrenaline has both alpha 1 and beta 2 action.
- Due to alpha 1 induced vasoconstriction, there is sharp rise in BP.
- Due to beta 2 induced vasodilatation, there is a prolonged fall in BP.
- If an alpha blocker is administered before adrenaline, there is only prolonged fall in blood pressure.
- This property is called **vasomotor reversal of Dale**. It is only seen when an alpha blocker is given along with adrenaline.
- If a beta blocker is given along with adrenaline; there will be a profound increase in BP due to unopposed alpha action.

Dilution of adrenaline

- It has three dilutions –
  - i. 1:10,000 – IV or intracardiac route
  - ii. 1:1000 – Intramuscular or subcutaneous route
  - iii. 1:100 – Inhalational route
  - iv. 1/50,000-1/2,00,000- +LA agent

Accident overdose of Adrenaline

Treatment: give both alpha + beta blocker

1.Propranolol + Phentolamine

Or

2.Labetalol (alpha and beta blocker)

Alpha 2 agonistic agents 00:31:41

Alpha 2 agonists

Oxymetazoline and Xylometazoline

1.Imidazoline compounds

2.alpha 2>alpha 1

3.Long duration of action.

On long term use (more often than every 3 hours/more than duration of 3 weeks)

–it causes ischemic damage to mucosa

-Impairs muco-ciliary clearance

-Rebound phenomenon

Dopamine

- Dopamine has two receptors - D1 and D2.
- D1 is a Gs coupled receptor present in renal blood vessels - It causes vasodilatation and diuresis.
- D2 is a Gi coupled receptor and a presynaptic receptor.
- At low doses dopamine has dopamine activity.
- At medium doses it has beta activity.
- At high doses it has alpha activity.

Peripheral action of dopamine

- Lose dose is 1-2 mg/kg/min infusion - Action on D1 receptor – Renal Vasodilatation - Diuresis. It is used in treatment of oliguria.
- Medium dose - 2-10mg/kg/min - Action on Beta 1 receptor - Heart rate is increased. It is used in treatment of congestive cardiac failure.
- High dose - >10mg/kg/min - Action on Alpha 1 - vasoconstriction - Increase in blood pressure - reflex decrease in heart rate.

Other drugs that can be included with dopamine are

i. Dobutamine - No activity on D receptors. Major activity on Beta receptors. Beta agnostic agent.; t half =2mins; achieves steady state in 10mins, so it is used in acute CCF

ii. Dopexamine – D1 activity with additional beta 2 activity.

iii. Fenoldopam – D1 activity with additional alpha 2 activity.

- Due to D1 activity there is vasodilatation, due to alpha 2 there is neurotransmitter release which further causes vasodilatation.
- It is used in hypertensive emergencies.

Treatment of hypotensive emergencies

- Phenylephrine, methoxamine, norepinephrine is used.
- These drugs are used because of activity on alpha 1 receptor.

Treatment of shock

Shock

+ I >VC	VC > + I
–Dobutamine	– Nor adrenaline
– Adrenaline	– Metaraminol (alpha +)

Treatment of chronic orthostatic hypotension

- Ephedrine, midodrine, fludrocortisone, or droxidopa can be used.

- **Fludrocortisone** is the drug of choice for neurogenic orthostatic hypotension.

Post-Prandial fall in BP

- Food intake -> Redistribution of blood to splanchnic area (splanchnic VD due to adenosine) -> decrease in peripheral blood flow -> decrease in blood pressure
- Rx: **Coffee-Methyl xanthines** produces antagonists' activity over Adenosine 1 receptor and prevents Splanchnic VD.

Beta2 agnostic agents

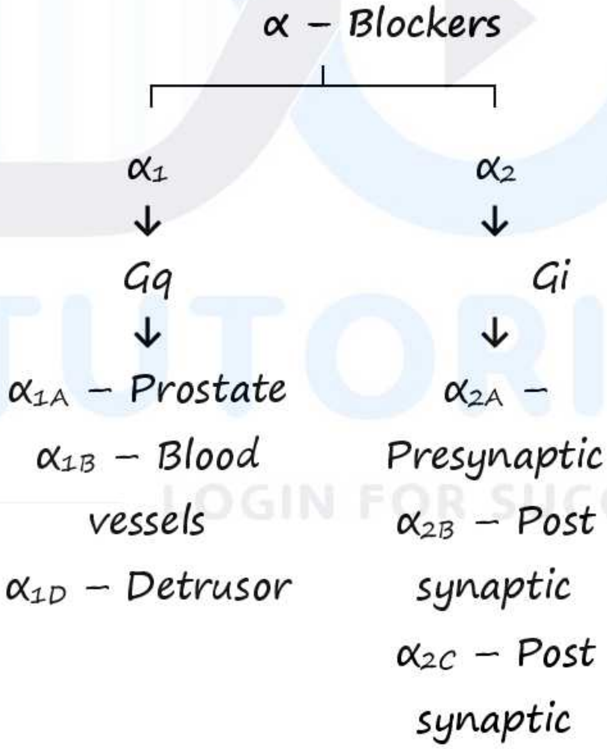
- Metaproterenol
- Salbutamol/Formoterol
- These drugs when given at high doses; selectivity is lost.
- These drugs are used for bronchial asthma.
- They act on beta 2 receptors on bronchial smooth muscles, and leads to bronchodilation.
- Stimulation of beta 1 causes increase in heart rate and it leads to tachy- arrhythmia.
- Tachyphylaxis and Tremors also occur due to beta 2 receptor agnostic action.

ANTI-ADRENERGIC PHARMACOLOGY

One liner:

- α-blockers with PDE⊖ - Prazosin
- Esmolol → shortest acting
- Metoprolol → more drug interaction even though least plasma protein bound
- β blocker with cocaine like effect → labetalol

α Blockers 00:02:44


α – Blockers
α₁
Gq
α₁A – Prostate
α₁B – Blood vessels
α₁D – Detrusor
α₂
Gi
α₂A – Presynaptic
α₂B – Post synaptic
α₂C – Post synaptic

A/E of α-blockers

- Vasodilation
  - Postural hypotension
  - Reflex tachycardia

- Increase urine output
- Nasal stuffiness
- Ejaculation abnormalities

Non-selective α Blockers 00:05:39

Non-selective α blockers

Phenoxybenzamine

- Highly lipid soluble
- Non-competitive, irreversible
- Partially bind with
- 5HT
- Histamine → sedation
- Muscarinic → anti-Ch. A/E
- No action on β receptors
- Veins dilated > arteries
- Shift of fluids
- Lungs → systemic
- Extra vascular → intra vascular
- Per oral (erratic per oral absorption)
- I.V – Long acting
- C.I – I.M/S.C – (extremely painful)

Phentolamine

- Competitive, reversible
- Only P.E (Rapid & short acting)
- Imidazoline derivative

  (also: Tolazoline

  ↓

  Partial α_1 agonist

  ↓

  Mild increase B.P)
- Used in D_x & R_x of pheochromocytoma
- Cheese reaction
- Clonidine withdrawal
- PIPE therapy
- P – Pharmacologically
- I – Induced
- P – Penile
- E – Erection

↓

"Cumulative toxicity"

↓

- Both produce
  - Reflex tachycardia
  - Postural hypotension

(also tetracycline)

↓

Phentolamine + papaverine

↓

Intra – cavernous injection

↓

Priapism

(Rx: Phenylephrine α_1 ⊕)

- Antagonize vasoconstrictor effect of soft tissue anaesthesia

Mechanism

Non-selective alpha blockers

α_1 ⊖

↓

Vasodilation

↓

Decrease BP

↓

Reflex increase HR

$\alpha 2$ ⊖

↓

No control of NA release

↓

⊕ β_1

↓

Increase HR

"Intense tachycardia"

Selective α Blockers 00:16:50

Selective α blockers

- zosin | - losin

1. Prazosin

$\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$

+

PDE 3/4 ⊖

Arteries > Veins

- Arteries Rx: HTN with BPH
- Veins A/E:

1st dose phenomenon (Postural hypotension)

↓

30% incidence rate

↓

"Tolerance develops"

Night time dosing

Uses

1. Scorpion sting
2. Favourable lipid profile

NS – β-blockers have deleterious lipid profile

3. Doxazosin
4. Terazosin

1. Tamsulosin

$\alpha_{1A} > \alpha_{1D} >>>> \alpha_{1B}$

Treatment:

BPH in normotensive

- No anti – HT
- No pro-apoptotic effect

A/E:

i. Retrograde ejaculation

ii. Dizziness

iii. IFIS (Intra-operative floppy iris syndrome)

2. Silodosin

↓

Uricosuric

↓

$\alpha_{1A} >> \alpha_{1D}$

A/E: Retrograde ejaculation (> Tamsulosin)

AfraTafreen.com
TUTORIALS
LOGIN FOR SUCCESS

- Pro apoptic effect on prostate

5. Alfuzosin → no anti – HTN effect

- QT prolongation
- $CYP3A_4$
- Since, CI with inhibitors of microsomal enzymes

Selective α_2 blockers

Competitive antagonist α_2 ← Yohimbine – aphrodisiac

↓

Congestion of genitals

A/E: Impotence

Tremor

Alfuzosin

i. Short acting.

ii. No anti-hypertensive effect.

Tamsulosin

i. Blocking activity alpha $_{1A}$ > alpha $_{1D}$ >>> alpha $_{1B}$.

ii. Alpha$_{1B}$ blocking is negligible so, it has no antihypertensive effect and no pro-apoptotic effect.

iii. Decreases tone of internal sphincter of bladder.

iv. Adverse effects:

- Dizziness.

  - Retrograde ejaculation.
  - Interop floppy iris syndrome.

Silodosin

i. Blocking activity alpha$_{1A}$ >> alpha $_{1D}$.

ii. Adverse effects:

  - Retrograde ejaculation.

Urapadil

i. Alpha$_1$ blocker.] Decreases B.P but there is less reflex increase increase H.R

ii. Weak β_1 blockade.

iii. Alpha$_2$ agonistic property.

iv. 5HT$_{1A}$ blocking property.

Alpha$_2$ selective blockers 00:27:16

- Yohimbine
  i. Competitive alpha$_2$ blocker
  ii. Additional 5-HT blocking
  iii. Causes congestion of genitals

Alpha blockers general effects

- General effects
  i. They tend to cause orthostatic hypotension. It occurs, as alpha receptors tend to cause

vasoconstriction whereas alpha blockers cause vasodilation.

ii. Vasomotor of dale.
  - It decreases the heart rate due to dilatation.

iii. Reflex increase in heart rate

iv. Nasal stuffiness

v. Miosis

vi. Na^+/H_2O retention

vii. Development

β-Blockers 00:28:13

Monotherapy C/I in HTN due to cocaine use

↓

Unopposed α induced VC

↓

Severe HTN

Non-selective β-Blockers 00:29:38

- Deleterious lipid profile

1. Propranolol

- Uses
  - Mnemonic: OP HAS ATM
  - O – Obstructive cardiomyopathy
  - P – Panic attack
  - H – Hyperthyroidism
  - A ⎤ Sub aortic stenosis
  - S ⎦

- A – Anxiety, akathisia
- T – Tremor (essential)
- M – Migraine (prophylaxis)

2. Esomolol

Shortest acting

↓

Esterase (from erythrocyte)

↓

≈ 10 min

- Treatment: HTN emergencies

Selective β-Blockers 00:35:20

Cardio selective	β B with ISA	β B with MSP
Mnem: ACNE @ BISME Acebutolol Nebivolol Atenolol Bisoprolol Metoprolol **Additional** • β_1 – Inverse agonist • Metabolised by CYP2D6 –Slow	Mnem: ACE PIN Acebutolol Celiprolol Pindolol ↓ B_1 ⊖ + PA β_2 Uses: 1. Exercise induced tachycardia 2. Safe in B.A	Mnem: ACE PROX Acebutolol Propranolol (max) Oxprenolol ↓ C.I in glaucoma (corneal anaesthetic property)

-Fast Uses: 1. Less Broncho constriction β_1 ⊖ → might evoke severe exacerbation of B.A 2. Safe with DM & HT 3. No effect -Lipid -Tremor	3. No effect - Lipid - Migraine	

Water soluble	Lipid soluble	Least PPB
Mnem: ABCS	Mnem: Less proper time	Mnem: M CAT
Atenolol	Propranolol	Metoprolol
Bisoprolol	Penbutolol	Celiprolol
Celiprolol	Timolol	Atenolol
Sotalol	Metoprolol	Timolol
↓	↓	
1. No CNS A/E 2. Nephron elimination 3. Longer acting	1. CNS A/E 2. Hepatic elimination 3. Short acting 4. More anti-arrhythmic	

Ocular selective
Mnem: Karthik believed me ↓ Carteolol Levobunalol Metipranolol

Impotency

- Less common than diuretics
  - i. High risk
    - Atenolol
    - Metoprolol
    - Carvedilol
  - ii. Low risk
    - Nebivolol

- Longest acting β-blocker – Nebivolol (11-30hrs) > Nadolol (20-24hrs)
- Shortest acting – Esmolol
- Most potent cardio selective β-B: Bisoprolol

Selective β-Blockers 00:35:20

Labetalol

- α_1 ⊖ (1/10th of phentolamine)
- β_1 ⊖ (1/3rd of propranolol)
- β_2 ⊕

- $\alpha_1 : \beta_1$ = 1:3 to 1:5
- Increase limb blood flow
- ⊖ N.A reuptake (cocaine – like effect)
  - DOC – HT in pregnancy

Carvedilol

- α_1 ⊖
- β_1 ⊖
- CCB
- $\alpha_1 : \beta_1$ = 1:1
- CYP2D6
  i. Slow
  ii. Fast
    - Anti-oxidant property

Nebivolol

- β_1 ⊖
- e NO synthase ⊕
- β_3 ⊕
- Increase insulin sensitivity
- Anti-oxidant property
- Causes rapid onset hypotensive response
- Least impotency

Celiprolol

- β_1 ⊖
- β_2 ⊕
- e NOS ⊕

- Anti-oxidant
- Papaverine like relaxant effect on vascular smooth muscle

Bucindolol – Increase HDL

Tilisolol – open K^+ channels

Effect on heart: β-blockers

i. Suppress
  - A – Automaticity
  - R – Renin release

ii. Lengthens
  - A – AV conduction
  - R – Refractoriness

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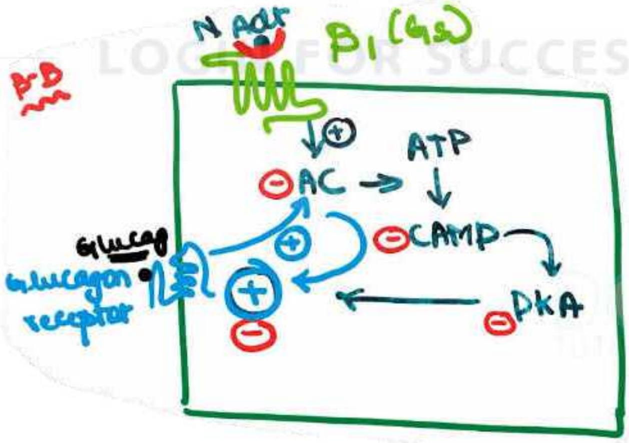
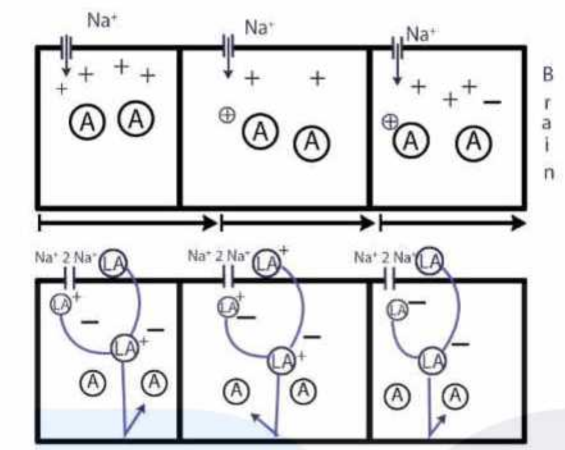
β-Blockers overdose 00:58:52


N Adr
β1 (Gs)
β-B
⊕
ATP
⊖ AC
⊖ CAMP
⊕
Glucag
glucagon receptor
⊕
⊖
⊖ PKA

LOCAL ANAESTHETICS

Incision



LA

↓

Drugs

Ester ('I')

↓

- Cocaine
- Procaine
- Chloropropane
- Benzocaine
- Tetracaine
  - Short and fast

↓

Metabolized to PABA.

↓

DI with sulfonamides

↓

- Short
- No PPB
- Plasma pseudo- ChE.
- More HS
- More cross sensitivity

↓

-all are VD.
-All less P.O BA
-All are metabolized by pseudo-chE.

-except cocaine

↓

-hepatic carboxyl esterase
-Partially excreted unchanged in urine

amide ('II')

↓

- lignocaine
- bupivacaine
- Dibucaine
- prilocaine
- ropivacaine

↓

-long
-PPB (d1-acid glyco protein
-Demethylation in liver
-Less HS
-Less cross sensitivity

↓

-less P.O Bioavailability
-high FPM
-Good absorption

Salient features 00:15:55

1.Stimulated > resting

2.Sensory= motor (except for Bupivacaine sensory > motor)

3.Decrease Ach release

4.Myelinated > non myelinated

5.Pain → temperature → touch → pressure

6.CNS → convulsions

7.CNS → cardiotoxicity (maximum: bupivacaine)

➔ Decrease BP → Vasodilatation (bupi > ligno)

↓

Ligno + Adr (1,50,000 to 2,00,000)

Advantage	Disadvantage
1. Increase duration of action	1. Increase edema/necrosis
2. Increase contact time.	2. Delayed wound healing
3. Increase intensity	3. Increase BP/arrhythmia
4. Increase toxicity	4. CI in digital block
5. Bloodless field for surgery	

Factors affecting onset of action

1. Concentration gradient: more concentration→faster onset of action.
2. Degree of ionization: maintain alkaline pH → more UI
   ↓
   Faster onset of action (OOA)
3. Solubility: mix LA with alkaline adjuvants → ($NaHCO_3$/Mg^{2+})
   ↓
   - Faster OOA

- Reduced concentration of lignocaine used
- Minimizes pain on injection
- Improves quality of block.

Bupivacaine 00:27:05

1) More lipophilic
2) Racemic mixture
3) More po

(<Dibucaine)
↓
Most potent
Longest acting
Most toxic

↓
Cardio-toxicity

- C.I in Bier's block
  ↓
  Ropivacaine
  (Less cardio toxicity)
  ↓
  Only S-isomer
  ↓
  -High therapeutic index
  -low toxicity.
- Levo-bupivacaine
  ↓
  Less cardio toxicity
- Treatment:
  Lipid emulsion.

4) Slow onset and long acting.

↓

Preferred in peripheral nerve blocks.

Neuro toxicity

Max: lignocaine and tetracaine

↓

Cauda equina syndrome

(or)

Transient neurological symptoms

↓

Patient usually recovers in 6-36 hours.

- Gastric / Duodenal ulcers → oxytocin
- Ophthalmic solution → proparacaine
- Methemoglobinemia → prilocaine and Benzocaine
- I.V regional anesthesia → lignocaine (Bier's blocker)

  also:

  - Mepivacaine
  - Chloroprocanie
  - Procaine
  - Etidocaine.

Maximum safe dose:

	Without adrenaline	With adrenaline
Lignocaine	5mg/kg	7mg/kg
Bupivacaine	175mg/kg	225mg/kg

BASICS – CNS BASICS

Neurotransmitter

i. Amine → Ach, Na, A, **DA → predominantly inhibitory**, H, 5-HT

ii. Amino acids

- Excitatory AA → Glutamate, aspartate
- Inhibitory AA → GABA, Glycine

iii. Peptides

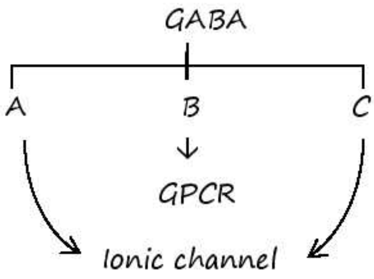
- Substance P
- Cholecystokinin

GABA 00:04:11

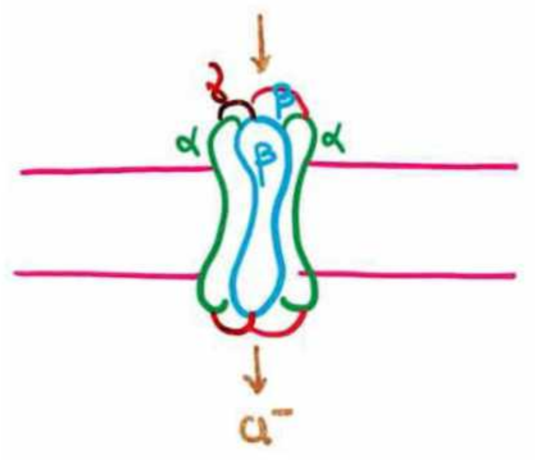
Synthesis

Glutamate ←
↓ Decarboxylase
GABA
↓ Transaminase
Succinic semi aldehyde
↓ Dehydrogenase
Succinic acid →

Receptors



GABA

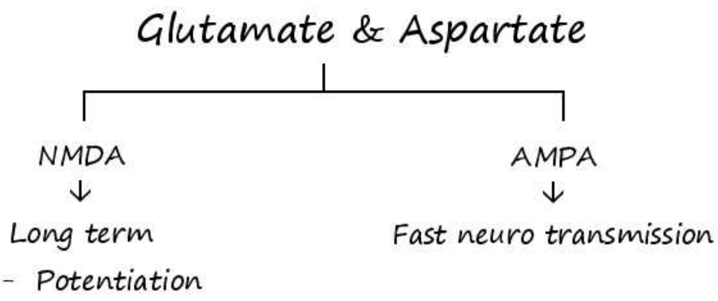


- GABA → 2α
- 'Z' compound → 2 α
- Benzodiazepines → α + γ
- Barbiturates → α + β
- General anesthetics → 2β

- EPSP – Excitatory post synaptic potential
  - Na^+ influx
  - Ca^{2+} influx
- IPSP: Inhibitory post synaptic potential
  - K^+ efflux
  - Cl^- influx

DOC TUTORIALS
LOGIN FOR SUCCESS

Glutamate & Aspartate 00:13:05


Glutamate & Aspartate

NMDA
↓
Long term
- Potentiation

AMPA
↓
Fast neuro transmission

SEDATIVE – HYPNOTICS

- Sedation → To reduce anxiety and to produce calming effect.
- Hypnotics → Induces sleep.

Barbiturates	Benzodiazepines
GABA mimetic & GABA facilitatory activity.	Only GABA facilitatory activity.
At high doses, they inhibit glutamate release and blocks AMPA receptors.	No action on glutamate.
Increases **duration** of chloride channel opening	Increases **frequency** of chloride channel opening.
Microsomal enzymes inhibition.	No action on microsomal enzymes (less drug interaction).
Dependence & tolerance are more in barbiturates.	Less dependence and tolerance in benzodiazepines.
No specific antidote- forced alkaline diuresis, **picrotoxin** (till pupillary reflexes are normal).	**Flumazenil** is the antidote (competitive antagonist).
Hyperalgesia + blisters for longer duration of use	Analgesia (no blisters).
Paradoxical excitation (idiosyncratic reaction)	No idiosyncratic reactions.

C/I in porphyria (AIP) as barbiturates increases ALA synthase	C/I in pregnancy, C/I in insomnia due to obstructive sleep apnea.
DOC for seizures in neonate's → phenobarbitone.	DOC for seizures in adults (emergency)→rectal diazepam.
Longest acting → phenobarbitone. Shortest acting → thiopentone (highly lipid soluble & high redistribution).	Longest acting → chlordiazepoxide & diazepam Shortest → midazolam.
In overdose → hypoxic + neurogenic drive.	In overdose → only hypoxic drive no neurogenic drive.

Benzodiazepines 00:09:00

GABA facilitatory

Mid brain	Limbic system	Medulla	Cerebellum
Sedative/ hypnotic	Anterograde amnesia	Muscle relaxant	Ataxia

- Aggravates sleep apnea (C/I is Insomnia due to OSA).
- C/I in pregnancy.
- Withdrawal seizures.

- Development of tolerance.

Decreases blood pressure

Decreases CO
↓
Diazepam, lorazepam

Decreases PVR
↓
Midazolam

- Short acting benzodiazepines →
- "LOTTE Choco pie".
- L – Lorazepam.
- O – Oxazepam.
- T – Triazelam.
- T – Temazepam.
- E – Estazolam

Safe in elderly/liver failure

- Oxazepam – active metabolite of diazepam.
- Lorazepam – stable absorption after IM route.
- Diazepam → adenosine agonist & hence causes coronary vasodilation.
- Prodrugs → prazepam.
  Clonazepam.

Salient features

1. Flunitrazepam
   a. Roofies
   b. Date rape drug
   c. Tasteless benzodiazepine

2.Most potent agent → Clonazepam

3.Most amnesia → Lorazepam (**anterograde**)

4.Longest → **Chlordiazepoxide> Diazepam**

5.Shortest → Midazolam

'Z' Compounds 00:17:05

- Drugs for insomnia.
- Z compounds bind to the GABA receptors almost in the same site where the physiological GABA blinds.
- Hence, it causes minimal sleep architecture and sleep hangover.

Z compounds

↓

GABA receptor @ $alpha_1$ subunits.

Zopiclone → To wean benzodiazepines

Zolpidem → safe in pregnancy.

Zaleplon → Shortest acting drug hence, used for initiating sleep

Eszopiclone is the longest acting agent hence, used for maintenance of sleep.

- No hangover, no withdrawal, no tolerance with the above drug groups.

Melatonin 00:19:55

- Secreted from pineal gland.
- MT_1 → responsible for sleep induction.
- MT_2 → responsible for circadian rhythm.

Agonists

- **Ramelteon** → (most common, Bioavailability of 2%) t1/2 of 2hrs, increases prolactin & decreases testosterone (mild S/E).
- **Agomelatin** – (additional anti-depressant).
- **Tasimelteon** (sleep – wake disorders in blind individuals)

Antagonists

i. Luzindole.

ii. Prazosin.

Orexin 00:28:40

Orexin – receptor type I or II antagonists

- **SUVOREXANT:**

- Can be used in Rx of insomnia.
- Adv reactions:
- Abnormal vivid dreams.
- Day-time somnolence.
- Depression (hence C/I in insomnia due to depression)

	0	1	2	3	4	REM
Barbiturates				↓	↓	↓
On discontinuation						↑
BZD			↑	↓	↓	↓
Nitrazepam				↑	↑	⇔
Eszopiclone			↑			

GABA-R

1. Muscimol –Agonist
2. Bicuculline- competitive antagonist of GABA-A
3. flumazenil-competitive antagonist of BZD binding site of GABA-A
4. Picrotoxin-Non-competitive antagonist
5. beta carboline -Inverse agonist (Pro-convulsant agent)

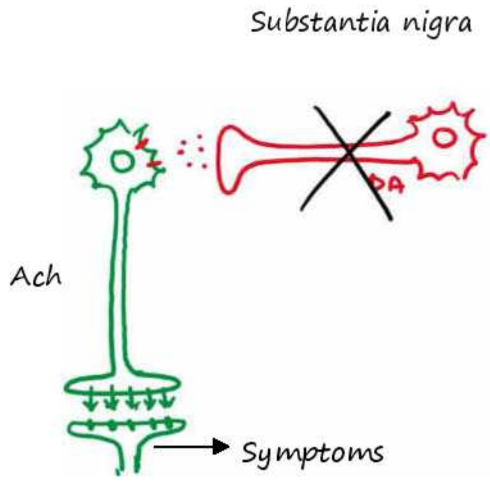
DOPAMINERGIC NEUROTRANSMISSION
(DRUGS FOR MOVEMENT DISORDERS)

Huntington`s Chorea 00:02:25

Huntington chorea

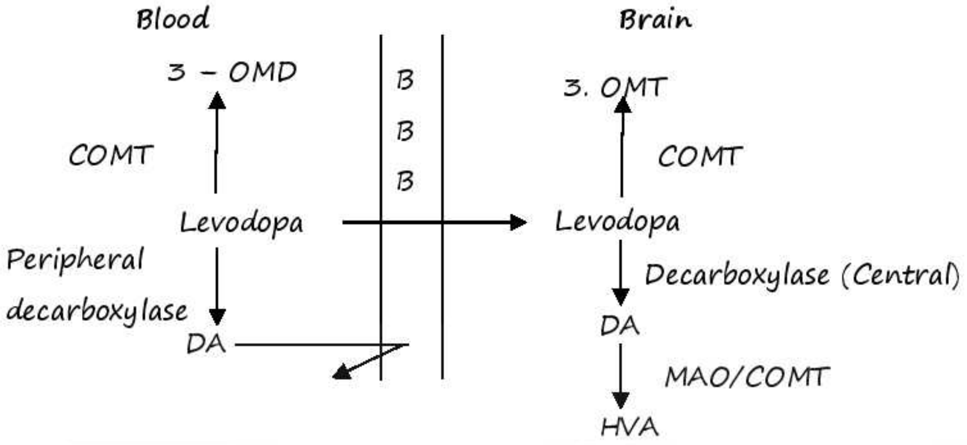
- Tetrabenazine
  - ↓ Reversible depletion of mono amines
  - ↓ A/E: depression
    - Postural hypotension
    - Parkinson's
    - ↓ C/I within 2 weeks of mono amine oxidase inhibitors
- Deu-tetrabenazine
  - ↓ Less A/E
- Haloperidol
- Quetiapine

Parkinson's 00:04:33



Treatment

- Increase DA
- Decrease Ach


Blood
Brain
3 – OMD
COMT
Levodopa
Peripheral decarboxylase
DA
B
B
B
3. OMT
COMT
Levodopa
Decarboxylase (Central)
DA
MAO/COMT
HVA

DOC
TUTORIALS

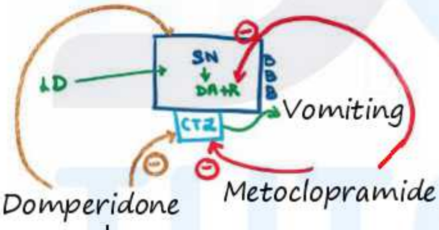
Treatment

- Increases DA
  ↓
  i. Levodopa
  ii. PDC ⊖
  iii. COMT ⊖
  iv. MAO ⊖
  v. DA +
  vi. DA facilitators
- Decreases Ach
  ↓
  Anti-Cholinergic drugs
  ↓
  Good central: peripheral ratio
  against
  ➔ Good: tremor, rigidity

Levodopa 00:15:25

- Bradykinesia → Rigidity → Tremor
  - General altering response → psychosis
  - Awakening effect in hepatic coma
  - "Dementia" does not improve
  - C/I with high protein diet & vitamin B complex (B_6) as absorption will be decreased
  - With non-selective MAO inhibitors –
    ↓
    HT crisis

- With Anti-Ch. → slows absorption of levodopa (Decreases GI motility)
- C/I in → Peptic ulcer
  → Acute narrow angle glaucoma
  → Malignant melanoma

A/E	
Initiation	**Long-term**
1.Nausea & Vomiting 2.Postural hypotension 3.Cardiac arrhythmia 4.Dysgeusia  LD SN DA+R BBB CTZ Vomiting Domperidone Metoclopramide ↓ Does not cross BBB → ↓ Efficacy of levodopa not altered	1. Dyskinesia - After few months - Dose limiting - No tolerance 2. Psychosis Rx. - Clozapine - Quetiapine 3.Mydriasis - CI glaucoma 4. "ON & OFF" ↓ Drug's effect i. short t½ of levodopa ii. Moment to moment synthesis of DA

Levodopa Induced Dyskinesia 00:29:00

Levodopa Induced Dyskinesia

- **Peak dose** ↓
  - Levodopa – dose reduced
  - COMT ⊖ / MAO ⊖ s
    ↓
    Switching to immediate release preparations
- **Off period** ↓
  - Long activity drug
  - During night Add DA ⊕/ COMT ⊖ MAO ⊖
- **Diphasic** ↓
  - Levodopa + Carbidopa As intestinal infusion
    (or)
    Sc. Apomorphine
    (or)
    Deep brain stimulation

Peripheral Decarboxylase inhibitors 00:32:33

- Carbidopa
- Benserazide

- All disadvantages are corrected except:
  - i. Dyskinesia
  - ii. CNS A/E
  - iii. Postural hypotension
- Pyridoxine reversal – Not seen with Carbidopa

COMT Inhibitors 00:35:15

COMT ⊖

Entacapone
↓
1. Short acting
2. – Peripheral COMT
3. A/E – Dyskinesia
   - Diarrhoea
   - Orange coloured urine

↓
Augments
levodopa + carbidopa
(dose of levodopa decreases)

Tolcapone
↓
1. Long acting
2. – Central & peripheral COMT
3. Fatal hepato

Common A/E
- Nausea, vomiting
- Postural hypotension
- Vivid dreams
- Hallucinations

DA ⊕

D_1 ⊕	D_2 ⊕	D_3 ⊕
- Apomorphine	- Bromocriptine	- Pramipexole
- Pergolide	- Carbergolide	
- Lergotrile	- Ropinirole	

- Rotigotine → TD patch
  → Banned due to – crystal formation

Ropinirole	Pramipraxole
- $CYPIA_2$	- Unchanged

- Profound hypotension
- Impulse control disorders

Apomorphine

↓

- S.C for off periods
- More n/v
- Used as emetic & impotence

Amantadine

Increases DA release

↓

Effect decreases after few weeks

A/E

↓

- Reversible headache
- Livedo reticularis (local NE release)
- CHF (edema)

- Depression in Parkinson → SSRI
- Drugs used for Dementia in Parkinson → Rivastigmine/Donepezil/mementine

Essential Tremor 00:46:33

- Usually treatment not necessary

↓

Propranolol

↓ If ineffective

- Primidone
- Alprazolam
- Topiramate
- Gabapentin

Tourette Syndrome 00:47:37

- Behavioral

- 1st line – Clonidine
  - Guanfacine
- Also – Tetrabenazine
  - Risperidone
  - Haloperidol
  - Botulinum toxin A

Myoclonus 00:48:49

- Treatment: DOC Valproate

  or

  Levetiracetam

  or

  Clonazepam

  Also: piracetam

  DOC: Myoclonus with anoxic brain damage – Oxitriptan

Restless Leg Syndrome 00:50:20

- Treatment: Iron sulfate
- Non ergot DA +

  ↓

  i. Ropinirole

  ii. Pramipraxole

  iii. Rotigotine
- Refractory: Oxycodone + naloxone → To prevent opioid induced constipation, we combine naloxone with oxycodone

DRUGS FOR PSYCHOSIS - I

Dopaminergic pathways 00:00:44

Dopaminergic pathways

- Mesolimbic pathway ↓ Overactive in psychosis(+vie)
- Nigrostriatal pathway ↓ Involved in extra pyramidal side effects
- Tubero-infundibular pathway ↓ Responsible for prolactin secretion
- Neocortical pathway ↓ Responsible for negative symptoms in schizophrenia

Anti-psychotic drugs 00:02:10

Classification of Antipsychotics

Class	Drugs
Typical (D2>5HT2A)	
Low potency	Molindone Chlorpromazine thioridazine
High potency	Haloperidol Fluphenazine

	Trifluperazine Thiothixene
Atypical (5HT2A>D2)	
Serotonin-dopamine agonists	Risperidone Sertindole Ziprasidone
Multi-acting receptor targeted anti-psychotics (MARTAs)	Clozapine Olanzapine Quetiapine
Combined D2/D3 antagonists	Amisulpride Remoxipride sulpride
Combined D2/D3 partial agonist	Cariprazine
D2 partial agonist	Aripiprazole Brexpiprazole
New	Paliperidone Iloperidone Asenapine lurasidone

- Typical antipsychotics have more D_2 activity
- Atypical antipsychotics have more $5\text{-}HT_{2A}$ activity
- Extra pyramidal symptoms are more with high potency typical antipsychotics

- Risperidone is the most potent atypical antipsychotic
- Brexpiprazole is a derivative of aripiprazole

Features of Newer antipsychotics:

1. Paliperidone –
   - Contraindicated in renal failure.
2. Iloperidone –
   - Postural hypotension
   - QTc prolongation
3. Asenapine –
   - Given sublingually
   - Metabolized by CYP enzymes
4. lurasidone –
   - Given with food
   - Partial 5-HT_{1A} agonist
   - Acts as antagonist at 5-HT_{2A} and D2 receptors

Typical Antipsychotics 00:07:15

i. Chlorpromazine –

- Blocks D_2 receptors in basal ganglia leading to extra pyramidal symptoms
- Blocks D_2 receptors in limbic area leading to antipsychotic effects
- Blocks D_2 receptors in pituitary leading to hyper prolactinemia

- Blocks D_2 receptors in CTZ causing anti-emetic effect
  - Antiemetic effect is seen in all typical antipsychotics except thioridazine
  - Maximum alpha blockade → chlorpromazine
  - Longest acting → penfluridol
  - Maximum anticholinergic side effects → thioridazine
  - Most potent Drug-Haloperidol

Alternate Routes of Administration: 00:09:52

Intramuscular depot

Typical	**Atypical**
- Haloperidol	- Aripiprazole
- Fluphenazine	- Olanzapine
- Flupentixol	- Risperidone
- Zuclopenthixol	- paliperidone
- pipotiazine	

- i.m depot is administered by 'Z' track technique as test dose and patient should be reviewed after 5days.

DRUGS FOR PSYCHOSIS - II

Atypical 00:00:08

- Clozapine: (least D2 blockade)
- Receptor blockers are
  - D4 > D2 > D1 (-)
  - α 1 (-)
  - 5HT2 (-)
- D2 blockade is directly proportional to potency of a drug and is directly proportional to EPS
- Adverse effect of Clozapine:
  - Agra → Agranulocytosis (Dose independent)
  - Close → Clozapine
  - Delhi → Dry Mouth (anti-Ch.)
  - Mumbai → Myocarditis
  - Pune → Positive and negative symptoms of schizophrenia
  - Other adverse drug reactions:
  - Seizures → dose dependant
  - Sialorrhea → because of anti-serotonergic effect Sedation - Most Common; Clozapine is not stopped suddenly patient will have rebound insomnia
  - How can we prevent it → always taper the dose.

Aripiprazole: 00:05:16

Aripiprazole

PA at GI receptor

- D2
- 5HT1A

Ant at GI receptor

- 5HT2A

- Is a Long-acting agent and has tendency for weight loss
- Also known as Serotonin – Dopamine stabilizer agent
- Brexpiprazole is a derivative

Different types of serotonergic receptors

- 5HT 1, 2, 3, 4, 5, 6, 7
  - 1 and 5 are Gi coupled receptors
  - 4, 6 and 7 are Gs coupled receptors
  - 2 is Gq coupled receptor
  - 3 is an ionic channel (IC)

Dopamergic receptors: D1, D2, D3, D4 and D5

- D1 and D5 are D1-like receptors → Gs coupled
- D2, D3 and D4 are D2-like receptors → Gi coupled

DRUGS FOR PSYCHOSIS - III

- We can classify all the adverse drug reactions into 2 classes:
  i. Due to monoamine receptor blockade
  ii. Not due to monoamine receptor blockade
- **Adverse effects Due to monoamine receptor block**
  i. D2 receptor blockade will cause extra pyramidal side effects
  ii. H1 blockade, patient develops sedation, weight gain(+5-HT)
  iii. M1 receptor blockade causes anticholinergic adverse drug reaction (constipation)
  iv. Alpha1 receptor blockade which causes orthostatic/postural hypotension.
- **Adverse effects not due to monoamine receptor blockage.**

Metabolic

- Weight independent hypertriglyceridemia
- Hyperglycemia

Cardiac

- Arrhythmia
- Sudden cardiac death (SCD)

Others

- Seizures
- Agranulocytosis
- Retinal pigmentation
- Photosensitivity
- Cataract development

Extra Pyramidal side effects are not seen with

i. Pimavanserin

ii. Aripiprazole

iii. Brexpiprazole

iv. Cariprazine

- Extra pyramidal side effects are Least with Clozapine.
- Adverse drug reaction not related to extra pyramidal side effects:

Mechanism	Adverse effect	Drugs	What next?	Treatment
H1 blockade	Sedation	Max: ChlorpromazineClozapine Quetiapine	Rapid discontinuation Not recommended (Rebound insomnia) Except for clozapine (Tapering done)	
H1 blockade +5-HT2c blockade	Weight gain	Max: Chlorpromazine Clozapine Olanzapine	Switch to weight neutral drugs	Behavioral therapy metformin
M1 blockade	Anti-cholinergic adverse effect (Constipation)	Max:Chlorpromazine Clozapine (Most) Nor quetiapine	Avoided in elderly with dementia /delirium	Stool softeners
Alpha 1 blockade	Orthostatic hypotension	Max: iloperidone Clozapine	Iloperidone – Slow titration of dose Clozapine – Avoided	i.Advice to patient. to get up slowly from lying posture Fludrocortisone
Metabolic	Weight independent Hypertriglyceridemia and hyperglycemia	Max: Clozapine, Olanzapine	HbA1c, FLP, Body weight before initiation of therapy Discontinuation of the therapy (Resolves in 6 weeks)	Diet exercise
Cardiac	Blockade of myocyte repolarization with rapid Current (Ikr) induced QT prolongation Arrhythmia and sudden cardiac death	Max:Thioridazine also: Pimozide IM Droperidol IV Haloperidol	Discontinue /change drugs	
Others	Seizure	Max:Clozapine (Dosedependent) Olanzapine Least: pimavanserin	Stop/change the drug	Valproate (Divalproex) CI: i. Carbamazepine ii. Phenytoin

Metformin

- It increases leptin levels
- It increases insulin sensitivity in hypothalamus
- It delays gastric emptying.
- By these 3 mechanisms metformin keeps the body weight natural.
- Weight gain is not seen with loxapine.
- Weight gain is least with haloperidol.
- Anticholinergic adverse drug reactions are maximum with thioridazine among typical anti psychotics.
- Extra pyramidal side effects and its features:

Days to weeks			
S. No	ADR	Features	Points
1.	Acute dystonia (1-5days)	Spasm of muscles of tongue, face, back and rarely oculogyric crisis	Young at more risk (10-19 yrs.)
2.	Parkinsonism (5-30 days)	Bradykinesia, rigidity, tremor, shuffling gait	Elderly at risk
3.	Akathisia (5-60 days)	Subjective or objective restlessness without anxiety or agitation	Least responsive to antiparkinsonian drugs
Weeks to months			

4.	Neuroleptic malignant Syndrome	Fatal, Extreme rigidity, fever, unstable BP, myoglobinemia	Can persist for weeks even after stopping anti-psychotic
Months to years			
5.	Perioral tremor	Late variant of Parkinson's	Rabbit syndrome
6.	Tardive dyskinesia	Orofacial dyskinesia, rare- Widespread choreoathetosis or dystonia	Elderly at risk movements disappear during sleep

Days to Weeks

- Treatment of acute dystonia: Anticholinergic agents.
- Drug of choice is Benztropine i.m. Or diphenhydramine im.
- Dose can be repeated when needed.

Treatment of Parkinson's

- If an elderly patient develops Parkinson's because of anti-psychotics, it is a compulsive need for dose reduction or change in therapy.
- drug used is Benztropine or Diphenhydramine
- Amantadine can be used for drug induced Parkinsonism

- It has less CNS adverse reactions
- It has good absorption when given per oral
- Renal clearance (50% drug reduction in renal failure)
- treatment of choice for akathisia:
- It is a compulsive need for dose reduction or change in drug therapy
- Drug of choice: propranolol, clonazepam can also be administered whenever the patient is having an acute attack.
- Beta1 selective beta blockers or water-soluble beta blockers are of no use in akathisia.

Weeks to Months

- The most fatal extra pyramidal side effect is neuroleptic malignant syndrome (NMS):
- It can persist for weeks even after stopping antipsychotic drugs.
- Treatment of choice:
- Stop the drug immediately
- Administer support care
- Bromocriptine is more effective than dantrolene
- General anesthetic drug induces NMS: dantrolene is more effective than Bromocriptine

Months to Years

Perioral tremor

- Late variant of Parkinson's also called rabbit syndrome
- Treatment of choice: Benztropine or Diphenhydramine
- Tardive dyskinesia:
- Treatment of choice -patient is switched to clozapine
- deutetrabenazine and valbenazine
- Deuterium increases the duration of action.
- Acts as long-acting agent
- Less toxicity
- Less drug interaction.
- Valbenazine is converted to an active metabolite,

  and this active metabolite is broken down further into inactive metabolite and is excreted in the urine with the help of cytochrome 2D6 and 3A4 enzymes.
- Valbenazine is contraindicated with microsomal enzyme inducers.
- Anticholinergic drugs are contraindicated in Tardive dyskinesia as they worsen the symptoms.
- If patient develops Tardive dyskinesia acutely then we administer BZD which is the treatment of choice.

Hyperprolactinemia 00:22:36

- Mostly seen with risperidone and paliperidone
- Management:
- Dose reduction
- Treatment: Bromocriptine is administered.
- For rapid reversal- drug discontinuation is treatment.

Clozapine induced agranulocytosis 00:24:14

i. Patient develops agranulocytosis

ii. Preventing the development of agranulocytosis

Patient develops agranulocytosis

- If WBC level falls below 2000/mm3
- Absolute neutrophil count falls below 500/mm3
- In such cases we
- stop the therapy and taper the dose to prevent the development of rebound insomnia.
- Monitor the levels of WBC daily till WBC >3000mm3
- monitor twice weekly till WBC >3500
- monitor weekly after WBC >3500
- If the patient is still not responding we administer
- G-CSF (Filgrastrin)
- Gm-CSF (Sargramostrin)
- Off label use- we can use lithium (lithium has ability to cause leukocytosis.)

Preventing the development of agranulocytosis

- 1-6months weekly monitoring must be done.
- 6-12months bi weekly monitoring must be done
- remainder of therapy monthly monitoring of levels of WBC is done
- Blood pressure and WBC must be monitored while administering a patient clozapine.
- Other adverse drug reactions.
- Chlorpromazine- has the tendency to cause photo sensitivity.
- Chlorpromazine- increases liver enzymes.
- Retinal pigmentation- is associated with thioridazine (high doses)
- Quetiapine- can lead to cataract formation so eye check up every 6months is indicated.

ANTI-MANIAC DRUGS

Preferred drugs for the treatment of Mania

- Per oral therapy (P.O) →
  - **Risperidone** with a mood stabilizer **Valproate/ Lithium** (least preferred is lithium, due to adverse reaction and need to do therapeutic drug monitoring)
- Parenteral route →
  - Haloperidol with a more stabilizer valproate/ lithium (olanzapine can also be given by parenteral route)

Lithium 00:02:07

- Lithium has got two mechanisms of action
- It acts as a mood stabilizer agent which means it can treat patient from mania and can also treat a patient who is in depression

Mechanism Of Action

- **Lithium got two inhibitory activities by two other mechanisms**
  - It inhibits inositol monophosphatase (IMP-ase)
  - It inhibits glycogen synthase kinase-3 (GSK-3)

- Inositol monophophatase (IMP-ase) inhibition **decreases the brain desired neurotic factor** (- IMPase → decrease BDNF)
- Inhibition of glycogen synthase kinase 3 (GSK-3) increases the brain derived neurotic factor (- GSK-3 → decrease BDNT)
- Brain derived neurotic factor is involved in the neuro protection and neuro-plasticity
- In case of mania, more amount of brain derived neurotic factor is released that is more amount of neuroplasticity so, lithium is given to decrease it
- **GSk-3 is used in the treatment of depression**
- **Lithium has got uncompetitive type of inhibition**
- Km & Vmax values are decreased

  Lithium

  ↓ Uncompetitive
- ⊖ ImP-ase → decrease BDNF → treatment: - Mania
- ⊖ Gsk-3 → increase BDNF → treatment: - Depression

Pharmacokinetics 00:05:08

- Good absorption through per oral route
- It has got very pot plasma protein binding (PPB)
- If drug has high plasma binding activity duration of drug action increase
- Protein bounded drug gets excreted slowly

- Poor or no plasma protein binding, neither metabolised
- **Narrow therapeutic index**
- **Need for TDM therapeutic drug monitoring**
- As lithium is a free drug and has poor PPB it gets excreted easily
- If a patient has lithium toxicity, dialysis can be done it is effective
- **Lithium is excreted by kidney (Dose reduction in Renal failure)**
- 80% of lithium gets reabsorbed in proximal convoluted tubule (PCT)
- Lithium is a single positive ion, which acts as sodium reabsorption channels, reabsorbs lithium to PCT
- Which is why more propensity to toxicity
  i. **Hyponatremia patients are more prone to lithium toxicity** in hyponatremia, blood sodium level is very less, as a compensatory mechanism reabsorption will be increased to maintain the level of sodium. As more amount of sodium is gaining entry, more lithium also gets absorb
  ii. More than 90% gets reabsorbed. This is why hyponatremia patients are more prone to toxicity
  iii. Sodium can be used for lithium toxicity but it is not drug of choice
- Time taken to reach a steady state is around 5days least preferred in acute Mania

- Therapeutic concentration: - (meq/L)
  - For prophylaxis/ Bipolar depression → 0.6-1.0 meq/L
  - To decrease relapse → 0.8-1.0 meq/L
  - Toxic doses > 1.5 meq/L
  - Death > 4.2 meq/L
  - Acute Mania → 1.0-1.5 meq/L (not preferred drug) for acute mania, it is the therapeutic concentration, have to maintained between the given value as it is a narrow index therapeutic drug

Adverse effects 00:14:00

- **4 major types of drug reactions**
  - Shaking of hands and body (tremors & seizures respectively). It is a proconvulsion drug
- In high doses it causes tremors
- **It increases: -**
  - C – Calcium → hypercalcemia
  - L – Leucocyte count → leucocytosis
  - U – Urine output (Lithium induced nephrogenic diabetes insipidus)
  - U_2 – Weight gain
- It decreases: -
- **Hair → Alopecia**
- Thyroid levels → hypothyroidism (rare)

i. Usually causes benign non tender enlargement of thyroid

- It flattens T waves
- Worsening of psoriasis
- Development of vasculitis and folliculitis → lithium induced acne

(osmotic/ $NaHCo_3$)

What's next?

ADR	WHAT NEXT?
Polyuria (Most common)	1st DOC – Amiloride (Once daily) • 2nd DOC – HCT (Decrease dose of lithium to 1/3rd
Dry mouth (Causes polydipsia)	• Sugarless gum • Glycerine/ Pilocarpine mouth wash
Tremor (Earliest)	• 1st DOC – Propranolol • 2nd DOC – Primidone/ Vit B6/ BZD • If tremor is due to anxiety • 1st DOC – BZD
Weight gain (Most distressing)	• Diet, exercise • Topiramate
Cognitive impairment	• Modafinil/ Armodafinil

Sexual dysfunction	• Aspirin (240 mg) • PDE-5 inhibitors (Sildenafil)
Acne	• Decrease dose • If more symptoms • Changes therapy
Psoriasis	• Inositol
Kidney dysfunction	• eGFR and lithium levels (every 6m)
Thyroid dysfunction	• TSH levels before and after therapy (every 6-12m) • No need for drug discontinuation
Parathyroid dysfunction	• Calcium levels before and after (yearly monitoring) • Severe • Change drug • Cinacalcet • Local/ subtotal Para thyroidectomy

Drug interactions of Lithium 00:26:20

Lithium induced lithium drug interactions

- Lithium actions can be increased by certain drugs & decreased by certain drug
- **Increased action by: -**
  - Heavy sweating

  - Increased by decreased clearance by thiazide diuretic which is more than potassium sparing diuretics which is more than loop diuretics (Thiazide > potassium sparing > loop diuretics)
  - Increased reabsorption done by NSAIDS (Indomethacin), ACE inhibitors (Lisinopril) & Hyponatremia
- Decreased actions by: -
  - Increased clearance by osmotic diuretics & also by Acetazolamide
  - Decreased reabsorption by hypernatremia
  - Decreased reabsorption by Theophylline + sodium containing antacids.

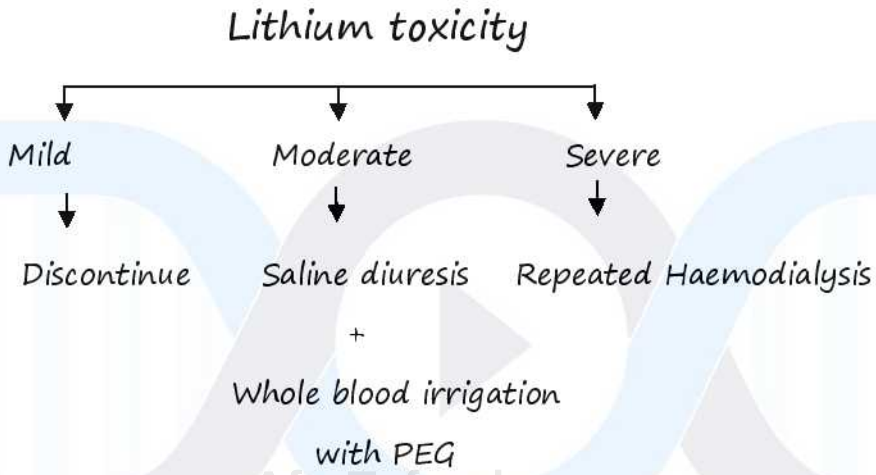
Lithium in pregnancy

- If we use in first trimester can cause Ebstein's anomaly
- It is a teratogenic effect, seen in foetus causing Atrial Septal defect (ASD) & displaces tricuspid wall
- If it is administrated in 24-48 hrs before delivery causes floppy baby syndrome and have propensity to cause fatal lithium concentration to increase

Toxicity of Lithium 00:31:02

- If mild toxicity, discontinues the therapy of lithium

- Moderate intoxication: - saline diuresis can administer osmotic diuretics/ sodium bicarbonates ($NaHCo_3$) + whole bowel irrigation with PEG (poly ethylene glycol)
- PEG binds with lithium and causes excretion and inactivates it
- In severe toxicity opt for repeated haemodialysis


Lithium toxicity
Mild
Moderate
Severe
Discontinue
Saline diuresis
+
Whole blood irrigation with PEG
Repeated Haemodialysis

Other anti-mania drugs 00:33:10

1. carbamazepine :>lithium – rapid cycles
<lithium-classic bipolar
No rebound mania

2. Sodium valproate and semi-sodium valproate: converted into valporic acid.
   - Advantages over Lithium: No need to TDM: no rebound mania
   - Baseline and periodic Investigations done before given valproate are CBC, LFT, BMI

3. Atypical anti psychotics

- Alanzapine
- Quetiapine- useful in prevention of depressive relapse
- Risperidone
- Aripiprazole
- Lurasidone
- Asenapine

4.Lamotrigene- depression>mania

Augmentation of effects of anti- mania drugs:

- Oxcarbazepine
- Gabapentin
- Clonazepam
- Verapamil
- Nimodipine

DRUGS FOR DEPRESSION - I

- The reason for depression is decrease in the excitatory neuro transmitters.
- Decrease in the happy hormones i.e. serotonin
- Serotonin is decreased in the pre synaptic terminal or decreased in the synapse.
- Primary aim in depression: increasing the level of serotonin and nor epinephrine in the synapse.
- This is done by
  - Inhibiting the reuptake of serotonin or nor epinephrine.
  - Blocking the metabolism of these drugs.

Drugs

Class	Drug
TCA	Dosulepin, Imipramine, Clomipramine, Desipramine, Lofepramine, doxepin, Nortriptyline, Amitriptyline
SSRI	Fluoxetine, paroxetine, Sertraline, Citalopram, Escitalopram, Fluvoxamine
SNRI	Venlafaxine, Duloxetine, Desvenlafaxine, Milnacipran

MAO inhibitors	Phenelzine, Tranylcypromine, Moclobemide (RIMA)
NRI	Reboxetine
NDRI	Bupropion
NaSSA	Mirtazapine
Melatonin agonist + 5- HT blocker	Agomelatin
Receptor blocking anti-depressant	Trazodone, Mirtazapine
Multi-modal	Vortioxetine

- Tricyclic antidepressants:
- They are of 2 different types:
  - Predominantly nor epinephrine TCA
  - Predominantly 5-HT TCA

Predominantly Nor-epinephrine TCA are

- Lofepramine
- Desipramine
- Nortriptyline

Predominantly 5HT TCA

- Clomipramine
- Desipramine can be used for cocaine dependence
- Nortriptyline can be used for smoking dependence

- Clomipramine is the only TCA used in OCD

Highest efficacy among TCA- amitriptyline used for nerve pain i.e. neuropathic pain.

Adverse effects of TCA

- Alpha1 blockade
- H1 blockade
- Muscarinic blockade

Alpha 1 blockade causes

- Postural hypotension
- Sexual dysfunction

H1 receptor blockade

- Sedation
- Weight gain (+5-HT blockade)
  - The weight gains and sedation is least with Lofepramine and imipramine
  - The weight gains and sedation is maximum with Imipramine and amitriptyline

Muscarinic receptor blockade causes

- Dry mouth
- Constipation
- Blurred vision
- Increased intra ocular pressure
- Urinary retention

- Cardiac arrhythmia
- The least anticholinergic adverse drug reaction is with Lofepramine
- Lofepramine is contraindicated in liver failure.

Toxicity

- Coma
- Convulsions- treated with benzodiazepine
- Cardio toxicity -treated by $NaHCO_3$, iv route.
- Therapeutic drug monitoring is necessary as all TCA have narrow therapeutic index drugs.

SSRI 00:10:45

- Fluoxetine- it is a long-acting drug as it has a long acting active metabolite.
- Fluvoxamine and paroxetine- both these drugs are short acting drugs. And have withdrawal symptoms (paroxetine > fluvoxamine).
- Least withdrawal symptoms are with Fluoxetine
- Fluoxetine and fluvoxamine both inhibit CYP2C19 enzymes.
- Fluvoxamine has additional inhibition of CYP1A2
- Paroxetine is the most potent SSRI

Uses of SSRI's

Mnemonic: Dr. Prescribes ABG for OP

- Depression (mild to moderate)
- Premenstrual symptoms
- Anorexia nervosa
- Bulimia nervosa
- Generalized Anxiety disorders
    - OCD
    - PTSD
    - Panic disorders.

Adverse effects of SSRI's

- Most common- nausea and vomiting, anorexia and dizziness.
    - Akathisia
- Sexual dysfunction- most common cause of non-compliance
- Rarely they may cause QT prolongation.
- Rarely they may cause Arrhythmia.
- Weight loss for 1year followed by weight gain.
- Paroxetine causes only weight gain no weight loss.
- Safest drug to give with warfarin is Sertraline and also citalopram

DRUGS FOR DEPRESSION - II

SNRI's (Serotonin norepinephrine reuptake inhibitor) 00:00:12

- They are 2 major drugs
  i. Venlafaxine
  ii. Duloxetine

Venlafaxine

- Venlafaxine causes more nausea and vomiting
- It inhibits norepinephrine reuptake so more amount of norepinephrine is present causing vasoconstriction hence it causes hypertension (most adverse)
- It is a faster acting drug and short acting agent
- It causes more withdrawal symptoms (flu like symptoms)

Duloxetine

- It causes early nausea and vomiting
- It causes constipation
- Duloxetine is used in the treatment of Diabetic neuropathy.
  - Venlafaxine and Duloxetine are the drug of choice for the treatment of severe depression.

Newer Antidepressants 00:02:35

Mirtazapine

- It belongs to a group called NaSSA drugs. (Noradrenergic specific serotonergic antidepressants)
  i. It blocks alpha2 hetero receptors
  ii. It blocks 5-HT2 receptors
  iii. It blocks 5-HT3 receptors
  iv. As it blocks 5-HT3 receptors it has additional anti-emetic property
  v. As it blocks alpha2 hetero receptors and 5-HT2 receptors it causes sedation and weight gain so it is used in treatment of depression with insomnia.

TUTORIALS
LOOK FOR SUCCESS

Trazodone 00:03:38

i. It blocks alpha 2 receptors
ii. It blocks H1 receptors
iii. It blocks 5HT- 2A/2C receptors
iv. It causes sedation
v. It causes priapism.

Agomelatin 00:04:07

i. It has got 5-HT2C blockade
ii. It has got melatonin receptor blockade
iii. It causes hepatotoxicity (liver enzymes must be monitored when patient is on Agomelatin)

Bupropion 00:04:40

i. It is a NDRI (norepinephrine dopaminergic reuptake inhibitor)

ii. It causes insomnia

iii. It is an epileptogenic

iv. It can be used for treatment of smoking cessation. (Choice of drug for smoking cessation is varenicline partial agonist agent of nicotinic receptors)

Vortioxetine 00:05:40

- It is multi modal therapy.
- It has Serotonin reuptake inhibition property (SRI)
- It blocks 5HT3 receptors
- It stimulates 5-HT 1A
- It causes sexual dysfunctions

DQT TUTORIALS

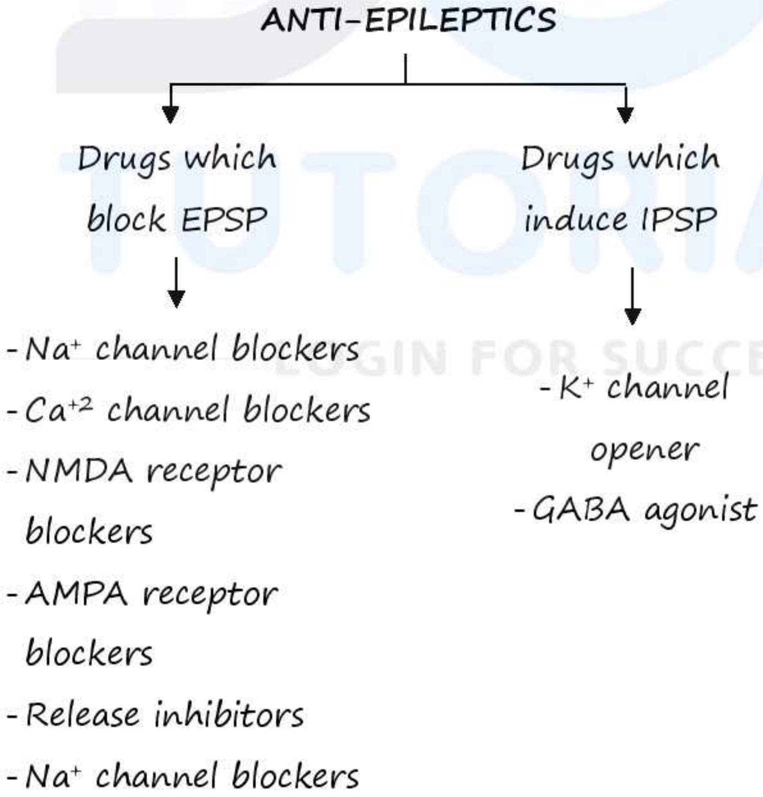
What next?

i. Patient is treated with SSRI but not responding
   - SSRI's take 3-4weeks for onset of action (this is called as Lag period)
   - If even after lag period, the pt. is not responding then we decrease the dose and change to SNRI or Mirtazapine.
   - Cross tapering must be performed to avoid withdrawal symptoms.

  - If we plan on giving irreversible MAO inhibitor there is no need of cross tapering, wash out period is required of 2-3 weeks
  - 4-5week wash out period for long-acting SSRI i.e. Fluoxetine
- If patient achieves remission
  - Treatment is continued for 9months
- Drugs used to augment the effect of SSRI's
  - Mirtazapine
  - Bupropion
  - Lithium
  - T3 (T3 is contraindicated with Lofepramine)
  - L-tryptophan
  - Pindolol (blocks the negative feedback of 5HT on 5-HT 1A receptors)

DRUGS FOR EPILEPSY – I

- Neurotransmitters which cause excitation
- Glutamate
- Aspartate
- Ions involved in excitation → Na^+, Ca^{2+}
- Neurotransmitters which cause inhibition
- GABA
- Glycine
- Ions involved in inhibition → K^+, Cl^-
- Anti-epileptics block all the excitation and induce the inhibition complexes



ANTI-EPILEPTICS

- Drugs which block EPSP
  - Na⁺ channel blockers
  - Ca^{+2} channel blockers
  - NMDA receptor blockers
  - AMPA receptor blockers
  - Release inhibitors
  - Na^+ channel blockers
- Drugs which induce IPSP
  - K^+ channel opener
  - GABA agonist

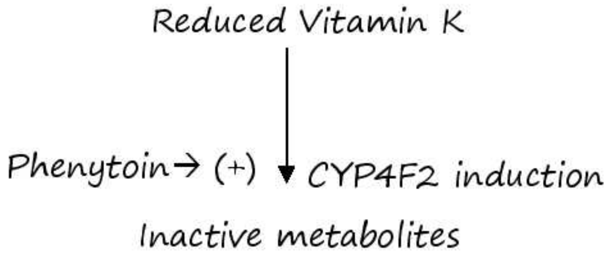
Phenytoin 00:01:50

- Blocks spread of seizure discharges rather than inhibition – acts on Na^+ channels in CNS (blocks
- Microsomal enzyme inducer
- Follows saturation on kinetics therefore, dose increments should be made smaller as dose increases
- Lipid soluble; cannot be given i.v
- Fosphenytoin, a metabolite is water soluble
- Uses

  1. 1st line therapy in status epileptics
  2. Cardiac arrhythmias
  3. Myotonic dystrophy

Adverse Reaction

1. Hirsutism
2. Osteomalacia → (necessitates Bone density scanning)
3. Lymphadenopathy
4. Diplopia, Nystagmus
5. Cerebellar ataxia, tremors, dyskinesia
6. Dupuytren's contracture (due to free radicals)
7. Gum hypertrophy (blockade of collagen formation)
8. Hemorrhagic disease of new born → Mechanism



DOC TUTORIALS
LOGIN FOR SUCCESS

9. Macrocytic/Megaloblastic anemia
10. Hyperglycemia + rash
11. If phenytoin is given i.v, it may cause cardiac arrhythmias and purple glove syndrome (Distal ischemia) (not preferred in female patients)

Carbamazepine 00:09:35

- It is the drug of choice for **partial seizures** and **trigeminal /glossopharyngeal neuralgias**
- Adverse effects (mnemonic "**BAD OATH**")
  - i. B→ Brainstem and cerebellar dysfunction
  - ii. A→ Anemia (Aplastic anemia)
  - iii. D→ Delusional Hyponatremia
  - iv. O → Osteomalacia
  - v. A → AV conduction decreased, Allergic Reactions (Steven-Johnson syndrome)
  - vi. T → Thyroid dysfunction
  - vii. H → Hepatotoxicity (It is a microsomal enzyme inducer)

- **Both phenytoin and carbamazepine contraindicated in myoclonus**

- Derivatives of carbamazepine

- Oxcarbazepine
  - Fast onset of action
  - More delusional hyponatremia

- Eslicarbazepine
- **Fast escalation of doses is possible with Oxcarbazepine and Eslicarbazepine**
- **Lacosamide**

Lacosamide

- Enhances slow inactivation of voltage gated sodium channels
- Enhances collapsing – response mediator– protein – 2 (Responsible for neuronal differentiation)

- Given through oral route as syrup and also i.v
- Adverse effects
  i. **PR prolongation**
  ii. Nausea, Vomiting, Headache
  iii. Suicidality
- It can be used to treat refractory partial seizures
- Headache is an important adverse effect because other antiepileptic's are used to treat migraines

Lamotrigine 00:16:48

- Sodium channel blockade
- Calcium channel blockade
- Blocks glutamate release
- It has interaction with microsomal enzyme inducers and inhibitors so, its dose should be reduced when

given along with inhibitors and increased with inducers

- It causes less sedation
- **Rashes may develop (Steven Johnson syndrome /Toxic epidermal Necrolysis)**
- Steven Johnson syndrome can be prevented by slow **introduction of drug and gradual escalation of dose** ("Start low, Go slow")
- **Safer drug to use in pregnancy**
- **Contraindicated in migraine as it also causes headache**

Rufinamide 00:20:30

- Similar action as Lacosamide
- Adverse effects include
- Leucopenia
- QT shortening

Calcium Channel Blockers 00:21:10

Gabapentin

- Blocks L Type Calcium channels and binds to α_2 r submit
- Crosses BBB/Lipid soluble
- Uses

  1.Partial seizures

  2.Neuropathic pain

  3.Restless leg syndrome (RLS)

Pregabalin 00:22:25

- Used to treat
- Neuropathic pain
- Anxiety

Ethosuximide 00:22:48

- Has propensity to block T-Type calcium channels
- **Used to treat Absence seizures in children more than 3 years of age**
- Adverse effects
- GI related
- Parkinson's
- Steven Johnson syndrome
- **Death may be due to Bone marrow depression**

DRUGS FOR EPILEPSY - II

Drugs effecting GABA levels of the body 00:00:10

TV	fell from	Top	& broke into 2 pieces
↓	↓	↓	↓
Tiagabine	Felbamate	Topiramate	BZD(Benzodiazepine)

Vigabatrin

Barbiturates

- All these have GABA related activity. Useful in the treatment of Epilepsy

Tiagabine 00:01:20

Tiagabine

- Tiagabine is a blocker of GABA transporter.
- It will prevent the Reuptake of GABA.
- Once in the nerves the GABA is getting released, it needs to interact with the receptors.
- Tiagabine will inhibit GABA T. Thus, it is a Reuptake Blocker.
- Tiagabine is a contra indicated in absence seizures.
- This drug itself is Epileptogenic it might induce epilepsy because of its actions.

Vigabatrin 00:02:40

- Important drug which is currently being used.
- It is a Non-competitive and Irreversible inhibitor of GABA transaminase.

- It is a metabolism inhibitor
- Adverse effects –
  - Irreversible Tunnel Vision, due to this, monitoring in every 6 months is necessary
  - Confusion
  - Weight gain
- Currently Vigabatrin is a **drug of choice for Infantile Spasm (associated with Tuberous Sclerosis)**

Felbamate 00:04:44

Felbamate

- It has two different mechanisms
- NMDA (–)
- GABA (+)
- It causes **severe aplastic anaemia and fatal Hepatotoxicity.**
- Thus, Felbamate is **never prescribed as first line therapy.**
- **It is used only in refractory cases**

Topiramate 00:05:40

Topiramate

- It has got top mechanism of action over the other drugs
- Topiramate has got Sodium channel blocker property (Na^+ CB)
- It blocks NMDA (–) receptors

- It has GABA (+) agonistic property
- It has got Carbonic Anhydrase Inhibitory property.
  - This is responsible for weight loss associated with Topiramate
  - Development of Anorexia and Renal stones
- Topiramate can be used for treatment of chronic migraine
- Adverse drug reactions like –
  - Cognitive impairment
  - Typically naming difficulty
  - Production of increase IOP hence this drug is contraindicated in Glaucoma.

Valproate 00:07:45

Valproate:

- Broad spectrum anti-Epileptic agent
- What are the different mechanisms of actions of Valproate?
- It has got Sodium Channel Blocker Na^+ CB
- It has got Calcium channel blocker Ca^{+2} CB
- It has got GABA-R (+) agonistic property and GABA transaminase inhibitory property
- Adverse effects are - it causes
- (V) – **Vomiting**
- (A) - **Alopecia**, hair loss. If the drug is stopped, the hair will grow back curly, Ammonia levels increase, i.e., Hyper Ammonia

- (L) - Liver Enzymes will increase
- (P) – Pancytopenia, Pancreatitis and development of PCOD
- (R) - Retention of fat and glucose, resulting in weight gain by the patient.
- (O) - Oedema
- (A) – Appetite Increase, which results in further weight gain
- (T) – Tremors occur. This drug is the most Teratogenic drug among all the anti-epileptic agents
- (E) - Enzyme inhibitory property

Some other drugs used of late to treat Epilepsy are

Levetiracetam	Brivacetam
blocker of SVP2A	Blocker of SVP2A & Na^+ CB (sodium channel Blocker)
Rx. This is a drug of choice in Case of liver failure Adverse drug effect in case of Pregnancy as it tends to cause **Anencephaly**. Dose reduction is necessary in Renal failure	Dose reduction in liver failure

- SVP – Synaptic Vesicle Glycoprotein

Perampanel 00:12:45

- This drug is a Non-Competitive and Irreversible – AMPA receptor antagonistic agents.
- used for Focal Seizures
- It causes drowsiness
- Monitoring of mental state is necessary as there are chances of development of psychosis due to depression

Ezogabine 00:13:30

- Is a Potassium channel opener K+ CO?
- Initially this drug was used in Focal Seizures in patients of more than 18 years of age
- Of late this is not used, as it causes blue discoloration of skin and Retinal abnormalities
- Monitoring is required every 6 months, as they are eye related
- There is Urinary Retention

What's next?

1.Carbamazepine

- what next if the patient is prescribed this drug and epilepsy is under control?
- After four weeks of therapy, the dose must be increased gradually

- As there will be auto induction of its own metabolism

2.Valproate:

- Is the patient being on valproate and is not under control

We can add two different sets of other drugs like

Lamotrigine	Topiramate
Phenytoin	Vigabatrin
Carbamazepine	Gabapentin
Then the dose of these 3 drugs Must be decreased	No need of dose reduction

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Valproate

- What if the patient develops Nausea and Dyspepsia on being treated with Valproate?

  -We have to administer enteric coated tablets, as it will prevent nausea
- What if the Liver Enzymes increase due to usage of valproate?

  -No need for dose reduction

  -As the increase of liver enzymes is reversible and is going to be transient

-Very rarely it ends up in liver failure, but has to be closely monitored

- Not preferred in females
- Other uses of Valproate – Mania

Pregnant Women: WWE (women with epilepsy)

What if they

Are planning for pregnancy	Complain of missed Periods
- Change the drug to a better one like Lamotrigine -The dose must be increased in the third trimester - Therapy drug monitoring to be done in the third trimester	- If they are already on an Anti-Epileptic drug, continue the same drug - Monitor for teratogenicity - We can add doses of Folic Acid 5mg/d or Vit K for the last 2 days before delivery. This will prevent post-partum Haemorrhage

OPIOIDS

Opioids
- Endogenous
- Exogenous

3 major opioid receptors

- μ → respiratory depression → maximum affinity is seen with β – endorphins
- δ→ Development of tolerance → encephalin
- κ(kappa) → Sedation → dynorphin

Opioids
- PK
  - P.O
    Bioavailability
    ↓
    Max:
    Methadone
    Min:
    Morphine
  - DOA
    ↓
    Max:
    methadone
    Min:
    Remifentanil
- ROA
  - IM/IV
    C/I in peripheral vascular diseases (acute trauma)
    C/I in head injury

Opioids sensitivity
Increase in neonates & adult

Adverse Reactions

- Tolerance develops excepts miosis & Constipation

Opioid agonists

1.MORPHINE

- i.m. /i.v. / P.O/PR/epidural.
- Metabolized by glucuronidation
- Converted to m-6-glucuronide (active)
- Poor P.O Bio availability.
- Water soluble metabolite

2. CODEINE → $\xrightarrow{\text{Cytochrome 2D6}}$ Morphine

↓ ↓

Weak μ affinity (poor High μ affinity

Analgesic when given as a Monotherapy, when given with Paracetamol→ strong analgesics)

3.METHADONE →

- Long-acting agents (maintenance therapy)
- High plasma protein binding

4.FENTANYL → short acting (in low doses)

- Long half-life (when given @ high doses)
- Highly lipid soluble
- Transdermal patch / Transmucosal/ oral for break through pain
- High potency.
- No increase in intracranial tension /no release of histamine

- Remi fentanyl → derivative of fentanyl
- Enter drug & hence its shortest acting drug

Partial agonist: (In cases of addiction) 00:09:30

---

i. BUPRENORPHINE → Buccal /IM/Iv/T.D

- At high doses → Respiratory depression

ii. MEPTAZINOL

- High efficacy
- Central cholinergic property

Mixed agonist & antagonist

@

K → PA
μ → weak antagonistic

		Potency
i.	Pentazocine →	< morphine
ii.	Butorphenol →	> morphine
iii.	Nalbuphine →	= morphine

- Pentazocine → increase BP & causes tachycardia → CI in MI
- Nalbuphine → causes Dysphoria
- All the above 3 drugs have less dependency, sedation psychotropic effects and respiratory depression.

Drugs with actions on other systems 00:14:00

i. **MEPERIDINE / PETHIDINE** → μ - agonists

- Anticholinergic
- Corneal anesthetic
- No increase in uterine contraction
- No neonatal side effects

ii. **TRAMADOL** → weak μ - agonists

- SNRI
- High incidence of Nausea & dizziness
- Epileptogenic property.
- Drug interaction with MOA inhibitors

iii. Opioid antagonists →

- No active metabolite
- μ agonist (stronger than tramadol)

  +

- SNRI.

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Opioid antagonists

i. **NALOXONE** → Pure opioid antagonist least P.O bioavailability

- Competitive antagonistic agent
- K, μ, δ, & sigma.
- Only parenteral route, short duration of action.
- Hence, multiple IV doses have to be administered.

- Oxycodone + Naloxone = increases P.O bioavailability→ more time in G.I
- Overcomes constipation S/E.
- Refractory Rest-less leg syndrome.

C/I

i. Head injury.
ii. Pulmonary dysfunction; except pulmonary edema.
iii. Hepatic / Renal dysfunctions.
iv. Adrenal / Thyroid deficiencies.
v. Pregnancy. (Neonatal respiratory depression or neonatal opioid dependence)

1. Pt on methadone → e. g: In cancer patients

↓

If patient complaints of break through pain

- Add a short acting drug. e. g: Remi fentanyl.
- Don't increase the dose

2. Pt on Buprenorphine → Partial agonist (strongest affinity)

↓

If respiratory depression. Occurs → P.T.O

↓

- No use with naloxone immediately
- Respiratory stimulant (Doxapram).

3. Naloxone → is used against poisoning of
   - Morphine

- Pentazocine
- Butorphanol
- Nalbuphine
- Pethidine

i. Management of opioid withdrawal

ii. Management of acute morphine overdose

NITRIC OXIDE

- Nitric oxide is a potent endogenous vasodilator Auto-coid.
- It is the most important factor responsible for hypo-tension and septic shock.
- Nitric oxide can be released out by two different mechanisms:
  i. Exogenous mechanisms
  ii. Endogenous mechanisms
- Exogenous mechanisms include:
  - Nitric oxide donors
  - Nitric oxide gas
- Endogenous mechanisms include:
  - Nitric oxide synthase activators-they increase NO levels

    They are: Ach, histamine
  - Nitric oxide synthase inhibitors-they decrease the NO levels

    They are: Hemoglobin

Nitric Oxide Synthase Inhibitors 00:09:23

- NO is synthesized in the blood vessels.
- Inside the blood vessels on the vascular endothelium there is arginine.

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- Arginine is acted upon by Nitric Oxide synthase enzyme which leads to synthesis of citrulline and Nitric oxide.
- This Nitric oxide is going to activate guanylyl cyclase.
- Once guanylyl cyclase is activated it converts GTP to cGMP
- cGMP causes Vaso Dilatation.

- Types of Nitric Oxide Synthase enzyme:
    - It can be of 3 different types:
        i. Isoform1
        ii. Isoform2
        iii. Isoform3
- Isoform 1 is also called as constitutive Nos (cNOS)
    - It is found in epithelial cells and neuronal cells they also secrete bNOS and nNOS
- Isoform2 is also called as inducible Nos (iNOS)
    - It is found in macrophages and smooth muscles they also secrete mNOS
- Isoform3 is also called as endothelial Nos (eNOS)
    - It is seen in Vascular endothelium
    - All these 3 different nitric oxide synthase enzymes synthesis Nitric Oxide.
    - The NO synthesized is not stored within the body.

Exogenous Nitric Oxide donors

i. Nitrates and nitrites: after administration it enters into blood, from the blood it crosses the endothelium and enters smooth muscles. Inside the vascular smooth muscles these nitrates and nitrites will release NO which causes Vaso dilatation.

   - MADH2 enzyme is necessary to release NO. (MADH2 is more in veins than arteries)
   - Same vasodilation is also produced by another drug that releases nitric oxide in the blood itself this drug is Nitroprusside.
   - Nitroprusside needs oxygenated Hb to release NO.
   - Arteries are more than or equal to veins in dilation as per when nitroprusside is concerned.

Nitric Oxide Synthase inhibitors 00:09:45

- They decrease the level of nitric oxide leading to increase in constriction of blood vessels.
- They have no clinical value.

NOS inducers

- Used for the treatment of angina
- Used for treatment of M.I
- Used for pre-eclampsia
- Used for pulmonary Hypertension
- Used in ARDS

INOMAX

- It is nitric oxide gas itself.
- It can be used in neonates with hypoxic respiratory failure. Used along with o2.

DRUGS AFFECTING VASCULAR TONE
(DRUGS FOR ANGINA)

Hemodynamic determinants

Wall Stress
Heart rate
Contractility

Wall Stress

i. Intraventricular pressure
ii. Ventricular volume
iii. Wall thickness

Anti-Anginal Drugs 00:07:23

↑ O2 supply	↓ O2 demand
Nitrates	Nitrates
Nitroprusside	β – Blockers
Sildenafil	Ivabradine
Calcium channel blockers	Ranolazine
Nicorandil	Trimetazidine

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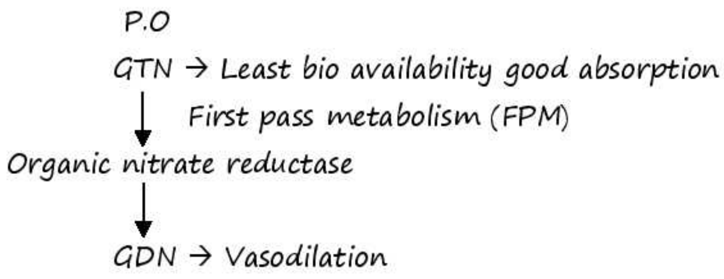
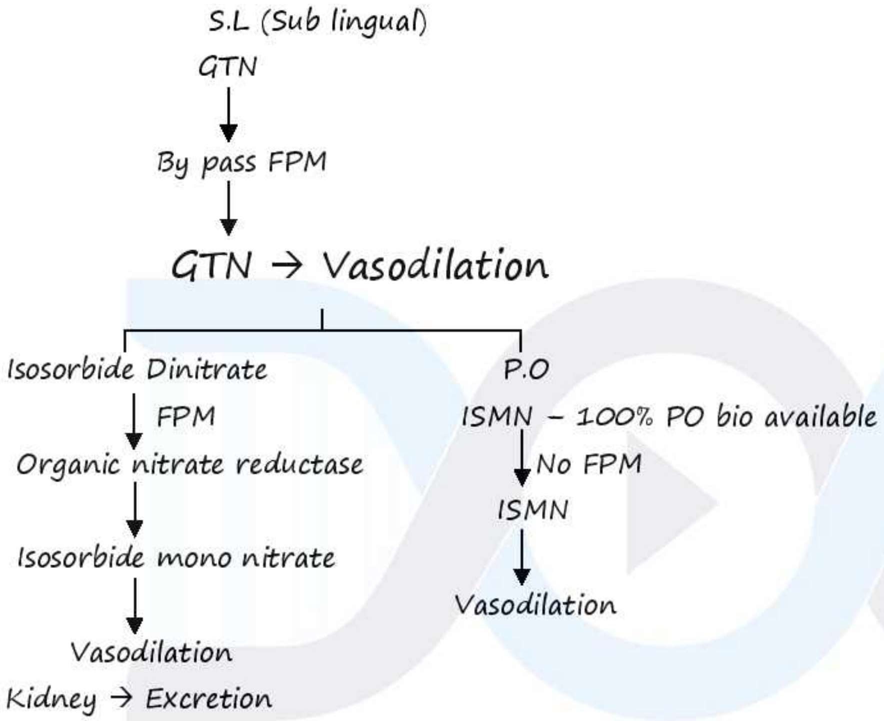
Nitrates 00:08:55

- Glyceryl trinitrate → PO/TD/SL/Buccal
- Isosorbide dinitrate → PO/SL
- Isosorbide mononitrate → PO
- Penta erythritol tetra nitrate → PO (Duration of >6hrs action)
- Amyl nitrate → inhalational (Rapid absorption)
- Keep at tightly closed containers → Highly volatile (Not light sensitive)


P.O
GTN → Least bio availability good absorption
First pass metabolism (FPM)
Organic nitrate reductase
GDN → Vasodilation

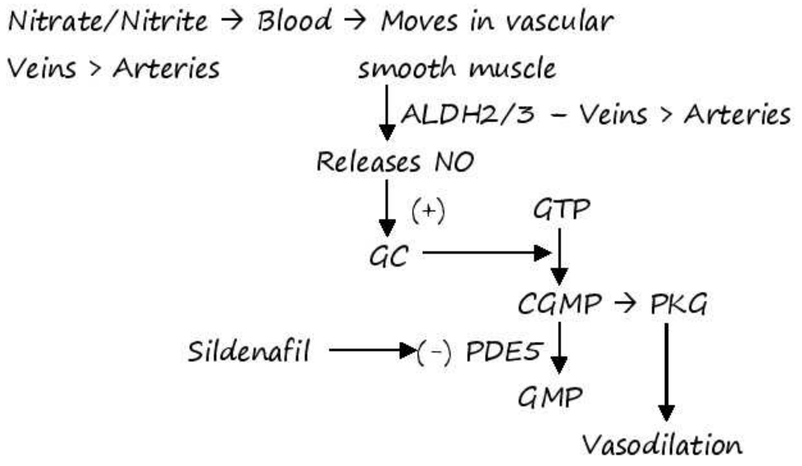

S.L (Sub lingual)
GTN
By pass FPM
GTN → Vasodilation
Isosorbide Dinitrate
FPM
Organic nitrate reductase
Isosorbide mono nitrate
Vasodilation
Kidney → Excretion
P.O
ISMN – 100% PO bio available
No FPM
ISMN
Vasodilation

Penta Erythritol tetra nitrate (PETN)

- PeTN → Longest acting
- PeTN > ISMN > ISDN

Mechanism of action

- No direct effect on cardiac/Skeletal muscle


Nitrate/Nitrite → Blood → Moves in vascular smooth muscle
Veins > Arteries
ALDH2/3 – Veins > Arteries
Releases NO
(+)
GC
GTP
CGMP → PKG
Sildenafil
(-) PDE5
GMP
Vasodilation

- Sildenafil CI with nitrates/Nitroprusside – cause profound hypotension

↓

Weak inhibitor of PDE-6

↓

Responsible for photo receptor signal transduction

↓ Due to blockers

Colour hues (or) Brightness

- Drug interaction occurs up to 24hrs

↓

Except tadalafil – up to 30hrs

Nitroprusside → Blood
Arteries ≥ veins ↓ O2 Hb
Release No
↓
Vasodilation

Nitrates
- Classical → ↓ Preload/↓ O2 demand
- Vasospastic → Vasodilation (Not effective in concentric atheroma)
- Unstable → 1. Vasodilation
  2. ↓ O2 demand
  3. ↓ Platelet aggregation

Nitroprusside → In Renal failure

↓ Causes cyanide Poisoning

↓ Accumulated
↓ Metabolized
Cyanide

- Disintegrates on light exposure

Tolerance

Mechanisms

- ↓ Tissue sulfhydryl
- ↑ O2 free radicals
- ↓ Availability of CGRP

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Prevent development

- P.O → Overnight nitrate free interval

↓

What if?

↓

Symptoms only during night

↓

Take tab on "quiet period" nitrate free interval during day time

- S.L → Spit out (Least chance)
- T.D (Trans dermal) → Most probable
  → Remove & uninstall patch weekly

Molsidomine – No tolerance

↓

Pro drug

Direct NO donor

- Dose must be tapered (Rebound ACs)
- Cross tolerance – Present

A/E:

- Postural hypotension
- Reflux ↑ HR
- Throbbing headache

] Tolerance develops

- Meth hemoglobinemia → Nitrites

↓

Rx: Cyanide poisoning

- Throbbing headache → Monday disease (Industrial exposure)

Nitrates

↑ Intra ocular Pressure
↓
Safe

↑ Intra cranial Tension
↓
CI

Nursing infants
↓
Intestinal flora
Inorganic nitrates (Well water) → Nitrate ions

Cyanide poisoning:

Hb
↓ Sodium nitrite (3% 10ml)
Methhemoglobin
↓ Cyanide
Cyan – methaemoglobin
↓ Sodium thiosulphate (25%, 50ml)
Meth haemoglobin + Sodium thio cyanate → urine
↓
Rx: Methylene blue (IV)

Nithiodote
↓
Replaced by
↓
Hydroxocobalamin 5g IV
→ More specific antidote
→ Red discoloration of skin & Body fluids

Uses

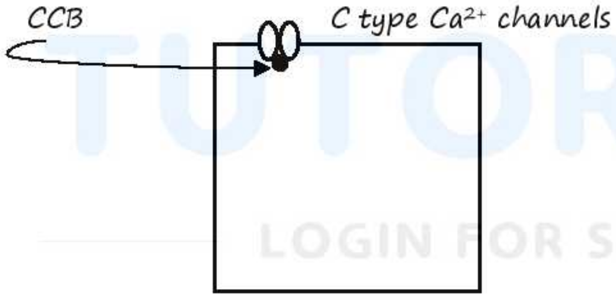
- Cyanide poisoning
- Acute coronary syndrome
- MI
- CCF
- Biliary colic
- Achalasia (Esophageal spasm)

Not ↑ Total coronary flow

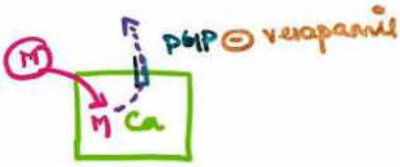
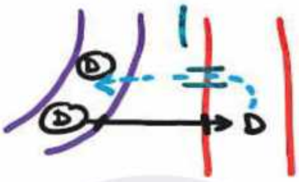
Redistribution occurs

Calcium Channel blockers 00:45:17

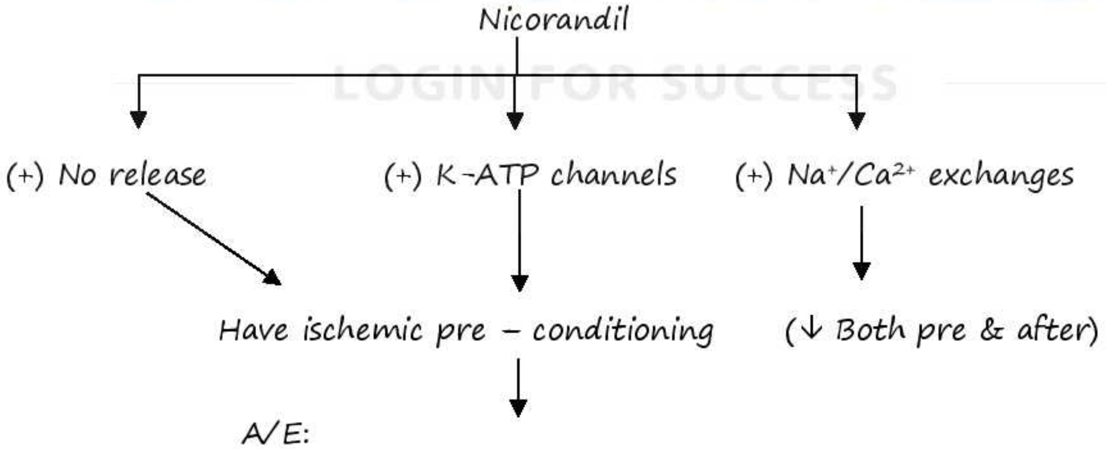
- Per oral (Verapamil – IV diltiazem)
- High first pass metabolism
- High plasma protein bound
- Nil effect on skeletal muscles



Dihydropyridines	Non – Dihydropyridines
- Dipines - Vascular > cardiac 1. Nimodipine – Only PO - IV – Cardiac arrest - cerebra selective 2. Nicardipine – IV/Intra cerebral arterial infection - Rx: Cerebral vasospasm	- Verapamil - Diltiazem - Etripamil (Nasal spray) → Used in SVT - Cardiac > vascular ((+) K^+ Channel block - (–) insulin releases

3. Amlodipine - Long acting - Safe in non-ischemic ventricular failure 4. Nifedipine - Shoet acting - CI in angina - Given as sustained release (Less chances of high HR) 5. Cilnidipine	- (-) P-Glycoproteins (Partially reverses resistance of anti - cancer drugs) - ↑ Digoxin concentration in blood   A/E - Constipation - (- Inotropic/Chronotropic/Dromotropic - Verapamil > Diltiazem → vasodilatory - verapamil > Dilatation - ↓ SA nodal automaticity V>D

Nicorandil 0057:43



Nicorandil

(+) No release

(+) K-ATP channels

(+) Na^+/Ca^{2+} exchanges

Have ischemic pre - conditioning

(↓ Both pre & after)

A/E:
GI ulceration (Buccal aphthous ulcer)
Skin & Mucosal ulcerations

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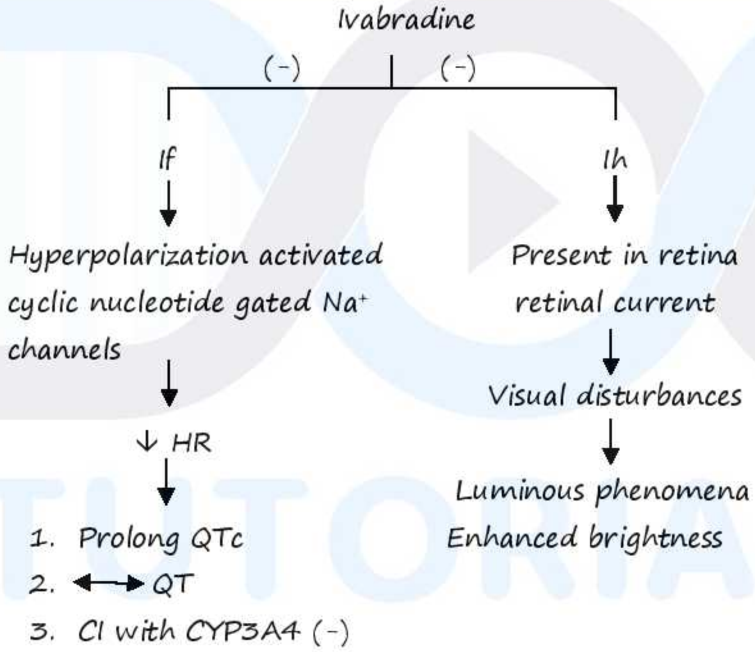
↓ O2 demand

β– Blockers

- CI in variant angina
- Usually prescribed with nitrates → Prevents reflex ↑ HR
- Only as prophylaxis
- Exercise induced tachy (-)
- Prolongs life in patients with cardiovascular disease

Ivabradine 01:02:20


Ivabradine
(-)
(-)
If
Ih
Hyperpolarization activated cyclic nucleotide gated Na⁺ channels
↓ HR
1. Prolong QTc
2. ⟷ QT
3. CI with CYP3A4 (-)
Present in retina retinal current
Visual disturbances
Luminous phenomena
Enhanced brightness

What next (2.5mg BD)

- >60 bpm → ↑ dose by 2.5mg up to max 7.5mg
- 50-60 bpm → Maintain dose
- < 50 bpm → ↓ by 2.5mg

If on 2.5mg

↓

Discontinue therapy

Ranolazine 01:07:23

- (–) late & prolonged Na+ current in myocardium

↓

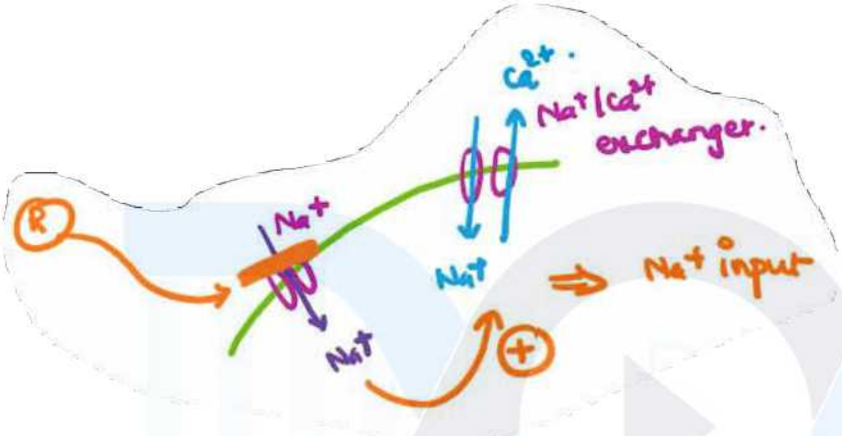
↑ Na+/Ca2+ exchanger

↓ Ca2+

↓ Intracellular Ca2+

↓

↓ Cardiac contraction



(–) Ionotropic → Ranolazine
(–) Chronotropic → Ivabradine

- Ranolazine → No alteration on Hr & BP

↓

Safe with sildenafil

- Use → 1. Chromic angina (No role in acute)
  2. CI: Severe renal failure & CYP34 (–) → Caution (Excreted via kidney)

Ranolazine → (–) metabolism of digoxin & simvastatin

In CAD patients ↓ QT prolongation

In heredity long QT ↓ QT shortening

Trimetazidine 01:14:32

Trimetazidine —(−)→ PFOX (Partial fatty acid oxidase)

Trimetazidine ↓ Parkinsons

PFOX ↓ (−) Inotropy

Coronary vasodilators

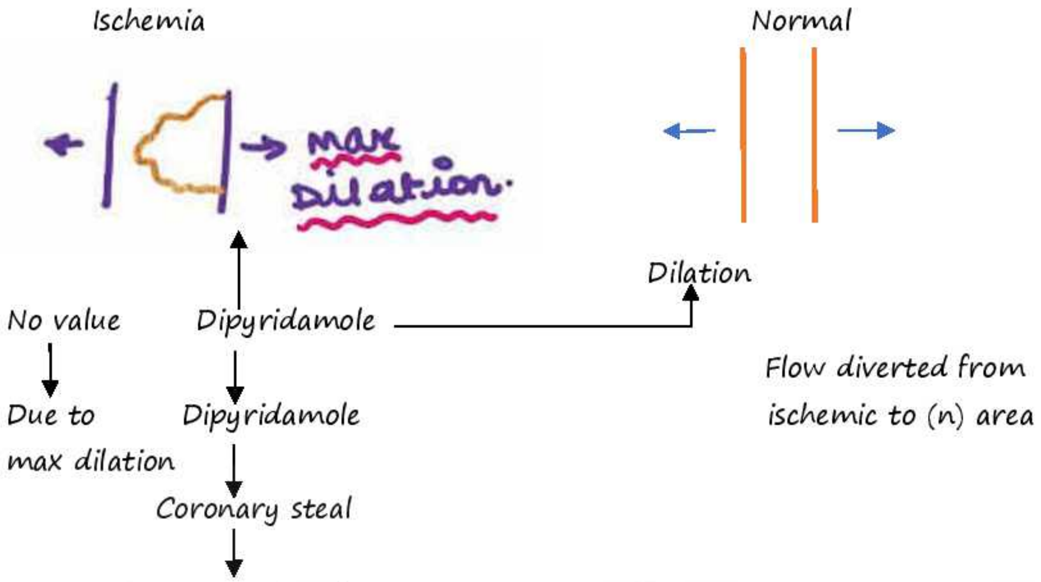
1. Dipyridamole
2. Adenosine analogues → a. Regadenosan → selective A2 A (+)
   - ↓ b. Binadensosan
   - c. Apadenosan

   Measures max coronary flow in pts with CAD (fractional flow reserve)

Dipyridamole

- (−) PDE ¾
  - ↓ CAMP → Vasodilation
- (−) Adenosine reuptake → ↑ extracellular Concentration of adenosine
  - ↓ ↓ Platelet aggregation

Coronary steal phenomenon


Ischemia
Normal
max Dilation.
Dilation
No value
Dipyridamole
Due to max dilation
Dipyridamole
Coronary steal

Flow diverted from ischemic to (n) area

Mnem: Die hard
D – Dipyridamole
I – Isoflurane
E – Enflurane
Hard → Hydralazine

New drugs

- P Kinase (–) + CCB = Fasudil
- Allopurinol

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Drug Combinations

Determinates	Nitrate (M)	CCB/β – Blocker	Nit + β blockers
Arterial pressure	↓	↓	↓
HR	↑	↓	↓
Contraction	↑	↓	↓/ ↔
EDV	↓	↑	↓

VASOACTIVE PEPTIDES

Vasoactive peptides act on blood vessels causing either

i. Vasoconstriction

ii. Vasodilatation

Vasoconstrictive vasoactive peptides 00:01:52

i. Angiotensin-II

ii. Endothelin

iii. Neuro peptide Y (NPY)

Vaso Dilatory vasoactive peptide

i. Bradykinin

ii. BNP/ANP

iii. CGRP

iv. VIP

Mixed Vasoactive peptides

- Substance P
  - The most important vasoconstrictive vasoactive peptide is Angiotensin-II
  - Most important Vasodilatory vasoactive peptide is bradykinin.

Vasoconstrictive Vasoactive peptides

Angiotensin-II:

- Angiotensinogen is converted to angiotensin -I by renin.
- Angiotensin-I is converted to angiotensin-II by ACE
- Angiotensin-II being a peptide is short acting and is broken down by peptidase enzyme angiotensinase.

Angiotensin-II acts at 2 receptors

i. AT1 and

ii. AT2 receptors

By acting on AT1 receptor angiotensin-II causes

i. Vaso constriction

ii. Increases release of aldosterone

  - Aldosterone release causes increase Peripheral vascular resistance (which further causes vasoconstriction)
  - Na+ and H2O retention

By acting on AT2 receptor angiotensin-II causes

i. Vaso dilatation by release of Nitric Oxide (seen in fetus and is responsible for fetal development)

  - In adults it is much lesser, in adults AT1 receptor dominates.

Renin inhibiting drugs

- Aliskiren
- enalkiren
- Rennikiren

ACE inhibitors

- Captopril
- Enalapril
- perindopril

AT1 receptor blockers

- Candesartan
- Telmisartan
- Valsartan

Endothelin 00:05:38

- It is a potent and a long acting vasoconstrictor agent. (More than Nor-epinephrine)
- It is synthesized from vascular endothelium.
- Types of endothelin are: ET1, ET2, ET3
- Receptors of endothelin are: ETA, ETB

Drugs

- ETA receptor is blocked by-
  - Bosentan
  - Ambrisentan

- ETA, and ETB receptors are blocked by macisentan
- Riociguat- it is a guanylyl cyclase activator,
  - Bosentan, ambrisentan, macisentan and riociguat all these drugs are used for Pulmonary hypertension
  - Currently bosentan is the 1st drug of choice for pulmonary hypertension.

Neuro peptide Y (NPY) 00:09:00

- It is a 36 amino acid peptide
- It is seen in CNS and in peripheral nervous system.
- It acts as a co-transmitter
- It is potent orexigenic agent(increases appetite) so any drug that blocks the NPY receptor can be utilized for the treatment of obesity.
- It is a potent vasoconstrictor agent.
- In NPY we have Y1 to Y6 receptors. Among these Y1 and Y5 are involved in orexia.

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Vasodilatory Vasoactive peptides 00:11:01

Bradykinin

- it is produced from kininogen.
- We have high and low molecular weight kininogen
- High molecular weight kininogen produces bradykinin
- Low molecular weight kininogen produces kallidin.

- Kallidin is acted upon by carboxy peptidase M/N and converted to active form Des-arginine-kallidin.
- Bradykinin is acted upon by carboxy peptidase M/N and converted to active form Des-Arginine-Bradykinin.
- The amino peptidase enzyme converts kallidin to bradykinin
- The amino peptidase enzyme converts des-arg-kallidin to Des-arg-bradykinin
- Des-arginine-bradykinin acts on B1 receptor
- Bradykinin acts on B2 receptors.

  And due to this B1 and B2 receptor action there is vasodilatation, Na+ / H2O excretion, cough and pain.
- Chronic pain is associated with B1 receptors.
- Acute pain is associated with B2 receptors.
- Angiotensinogen is converted to Angiotensin-I by Renin.
- Angiotensin-I is converted to angiotensin-II by ACE
- angiotensin-II acts on AT1 receptors and causes vasoconstriction and Na+ and H2O retention.
- ACE breaks down bradykinin to inactive metabolites and due to this breakdown the vasodilatation, sodium and H2O excretion, pain stimulation, and cough presentation is weaned off.

And vasoconstriction will predominate and sodium and water retention will predominate if the system is going to be continuously active.

CPM/N	ACE (PDP)
Breaks down bradykinin to active metabolite	Breaks down bradykinin to inactive metabolite
Also called as kininase enzyme, Kininase-I	Also kininase enzyme but it is kininase-II

- T1/2 of kinins in plasma is 15sec.

Drugs

kallikrein inhibitors:

i. Aprotinin
ii. Ecallantide
   - Both these drugs were previously utilised for angioedema (now discontinued)
   - Aprotinin is a natural Proteinase inhibitor.

Kinin receptor antagonistic 00:19:37

i. Icatibant - is a selective B2 receptor blocker. Given via sub cutaneous route.
   Used in acute episodes of hereditary angioedema.
ii. Natriuretic Peptides:

- 3 major types of natriuretic Peptides
  - Atrial natriuretic peptide (ANP)
  - Brain derived natriuretic peptide (BNP)
  - C-type natriuretic peptide

- All 3 are vasodilative causing peptides.
  - ANP and BNP act on cells (cardiac renal etc).
  - On the surface of these cells we have a receptor ie. natriuretic peptide receptor.
  - ANP or BNP bind to this receptor, and this receptor is associated with guanylyl cyclase.
  - Due to the activation of Guanylyl cyclase there is conversion of GTP to cGMP.
  - cGMP is in turn associated with Vaso dilation sodium and water excretion ie. natriuresis and diuresis.
  - ANP and BNP are peptides so they are broken down by peptidase enzymes and that enzyme is Neutral Endo Peptidase enzyme (NEP)

Drugs

i. ANP analogues: urodilantin, carperitide
ii. BNP analogues: Nesiritide
iii. Urodilantin analogue: Ularitide
iv. NEP inhibitor: Sacubitril, Racecadotril

  - Urodilantin, carperitide, nesiritide, ularitide and sacubitril – all these are utilised for the treatment of Congestive Cardiac failure.
  - Racecadotril – is utilised for treatment of acute secretory diarrhea.

CGRP (calcitonin gene related peptide) 00:24:36

- Calcitonin gene related peptide is a potent vasodilator.
- It is the most potent hypotensive agent/ vasoactive peptide
- May lead to reflex tachycardia.
- Vasodilatation can lead to 2 major conditions

  i. orthostatic hypotension

  ii. Migraine due to vasodilatation

  - Anti cGRP monoclonal antibodies: it breaks down cGRP and causes vasoconstriction.
  - E.g. Erenumab, Pramenezumab, Galcanezumab – all these drugs can be used for the treatment of episodic migraine (prophylaxis) given via sub cutaneous rote. Monthly single dose.

Vasoactive intestinal polypeptide (VIP) 00:27:07

- It is an extremely potent Vaso dilator agent for the intestines.
- It acts as a neurotransmitter
- It has 2 receptors Vpac1 and Vpac2

- VIP is a physiological hormone it is a vasodilatory vasoactive peptide, and universal hormone inhibitor is somatostatin.
- Somatostatin is found to decrease the activity of VIP and by administration of octreotide which is a somatostatin analogue it blocks the activity of VIP so the patient with GI bleeds(varices) can be treated with somatostatin and octreotide.

Mixed Vasoactive peptides

- Neurokinin- also called as tachykinin
- They are 3 different types of Neurokinins:
  i. substance P
  ii. neurokinin A
  iii. neurokinin B
- All these 3 act at 3 different kinds of receptors i.e.
  - Neurokinin 1 -Receptor
  - Neurokinin 2 -Receptor
  - Neurokinin 3 –Receptor

Functions

- Substance P:
  - It has mixed vascular effects
  - It is a potent arteriolar dilator
  - It acts as a Venoconstrictor
- neurokinins A and B cause nausea and vomiting.
- Drugs pertaining to Neurokinins:

i. Aprepitant – it is an NK1 receptor antagonist

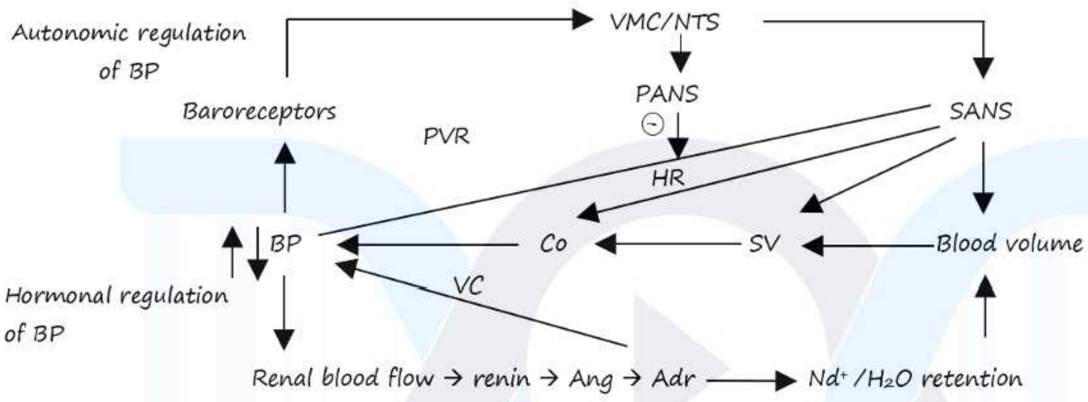
ii. Fosaprepitant – it is a pro drug, can be given via parenteral route.

  - It acts as NK1 receptor antagonist so both Aprepitant and Fosaprepitant can be used for treatment of chemotherapy induced nausea and vomiting (delayed type of CINV)

ANTI-HYPERTENSIVE DRUGS

Hypertension 00:08:36

- Autonomic regulation of BP -


Autonomic regulation of BP
VMC/NTS
PANS
SANS
Baroreceptors
PVR
HR
BP
Co
SV
Blood volume
VC
Hormonal regulation of BP
Renal blood flow → renin → Ang → Adr
Nd⁺ /H₂O retention

Autonomic regulation of blood pressure

- Hormonal & autonomic regulation of blood pressure only compensatory mechanism that the brain has for increased blood pressure is through activation of parasympathetic system and thereby decreasing the heart rate through ACH release.

Sympathoplegic drugs 00:12:21

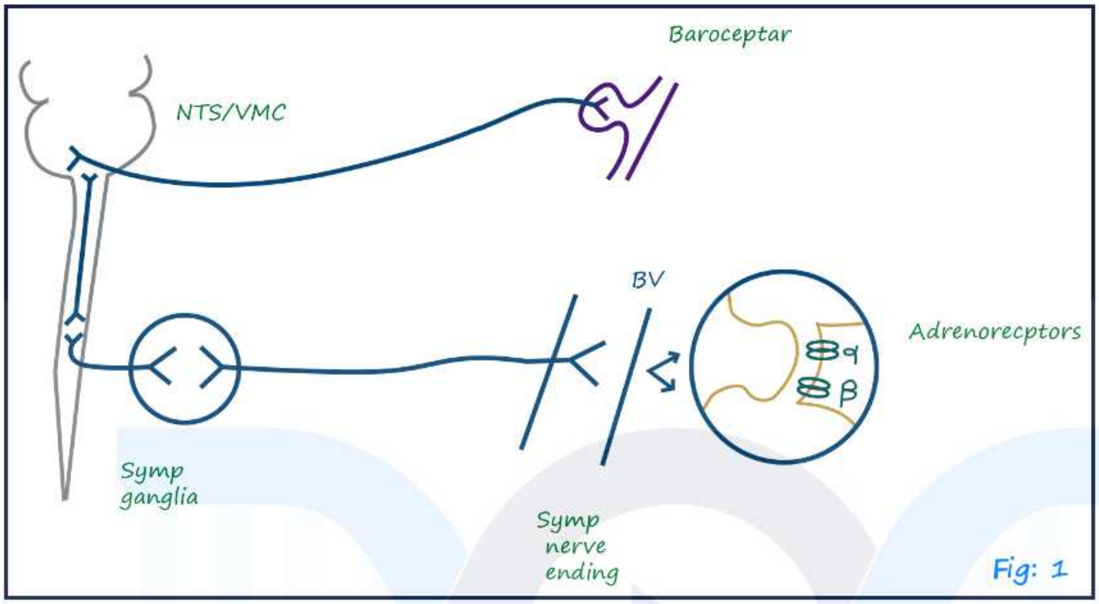

Baroceptar
NTS/VMC
BV
Adrenorecptors
α
β
Symp ganglia
Symp nerve ending

Fig: 1

- Veratrin alkaloids -
- Inhibit baroreceptors.
- Central sympathoplegics –
- Clonidine.
- Methyldopa.
- Drugs blocking sympathetic ganglia –
- Hexamethonium.
- Drugs blocking sympathetic nerve endings –
- Reserpine.
- Guavethidine.
- Drugs blocking adrenoceptors –
- Alpha and β blockers.

Clonidine and methyldopa 00:16:43

- Act as $alpha_2$ agonist when given P.O.
- Once they gain entry into the CNS, they act differently.

CNS

Clonidine

i. P.O → agonist @ $alpha_{2}A$ receptors → decreases BP.
ii. I.v → agonist @ $alpha_{2}B$ receptors → transient increase in BP.

↓

On withdrawal, causes rebound HTN Rx→ phentolamine.

↓

Used for diagnosis of pheochromocytoma (clonidine suppression test).

↓

Decreases HDL, $apoA_1$, A_2 (nil effect on the other lipids).

- MC adverse reaction → sedation.
- Dry mouth.
- Impotency.
- Additional/Imidazole agonist property (minor).
- Moxnidine & rilmenidine have major imidazole agonistic property both have long t1/2.

methyldopa (prodrug)

- No imidazole actions.
- Hematologic immune toxicity a.k.a positive

Noxonidine & rilmenidine:

- Long t1/2.
- Lesser adverse drug reactions.

- Treatment of diabetic diarrhea.

Anti-hypertensive drugs that are safe in pregnancy: 00:24:50

Pregnant → Prazosin

Hypertensive → hypertension

lady → Larine (hydralazine less postural (more arteriolar dilation than vasodilation)
Dy → Dihydropyridines → stopped before labor because they weaken uterine contractions.

choses → clonidine

Dolor → DO → Dopa (alpha – methyldopa).
CO → Labetalol.

Hydralazine

- Arteriolar vasodilation > venular vasodilation.
- Coronary dilation/cerebral/renal > cutaneous blood vessel dilation.

Hypertensive emergency

1. Esmolol – (ultrashort acting beta – blocker).
   - Short acting as it is broken down by plasma esterase enzyme.

- Used in cases of hypertension with aortic dissection.

2.Labetalol – (alpha + beta blocker)

- Doc for hypertensive emergency in pregnancy.

3.Nitroglycerine –

- CI in acute heart failure.

4.Nitroprussides –

- Doc for hypertensive emergency in non-pregnant individuals.
- Cautions whenever there in increase ICT.

5.Clevidipine –

- Broken down by esterase enzyme.
- Rapid onset of action.

6.Nicardipine –

- Cautions when used in coronary ischemia.
- CI in acute HF.

7.Enalaprilat –

- I.V drug → ACE inhibitor → in case of HTN + left ventricular failure.

8.Fenoldopan –

9.Vasoactive peptides –

- Physiological peptides that are innate to our body which produce vasoconstriction or vasodilation, thereby, affecting blood pressure.

Vasoactive peptides (VAP)

Vasoactive
↓
Angiotensin II
Endothelin
Neuropeptide
BNP
VIP

vasodilation
↓
Bradykinin
calcitonin gene related peptides (CGRP)
ANP

Pulmonary hypertension 00:31:12

1.Endothelin antagonist: "entrant" drugs
- bosentan
- Ambricentan
- macisenatan

2.prostacyclin (PGT_2) analogues:
- Epoprostenol → Iv infusion pumps approved.
- Treprostenol.
- Iloprostenol → Inhalational.

3.CCB

4.PGI_2 agonistic agents: selixipag.

5.PDE_5 inhibitor → sildenafil, tadalafil

6.Soluble gauntly cyclase activator→ "Guat" drug riociguat.

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DOC

- Intravenous vasodilator challenge

If positive → CCB is given

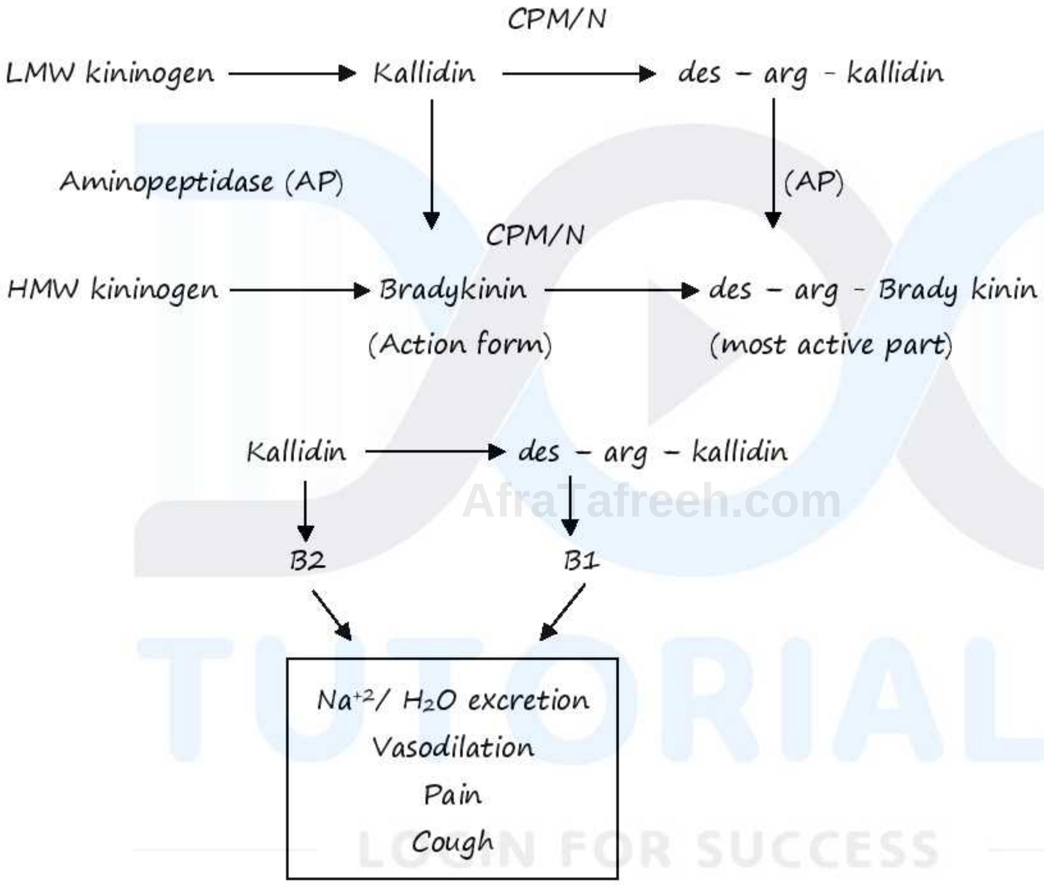
If negative → Bosentan is given

Diuretics in hypertension 00:37:41

- Thiazide diuretics (are preferred)
  - Decrease peripheral vascular resistance
  - Chlorthalidone (long acting) > HCT
  - Adverse reaction → Metabolic side effects also (increase in bl. glucose & lipids)
    i. Impotency (Thiazides > β blockers)
    ii. Decreased ECF volume (compensatory mechanism)
    iii. Hyperuricemia (contraindicated in patients with HTN and Gont)
  - Loop diuretics: less anti HTN than thiazides.
  - K^+ sparing diuretics:
    i. Usually given in combination with thiazides to compensate hypokalemia.
    ii. Spironolactone is least preferred → because of its anti-androgenic property.

1.Bradykinin:

- Synthesized from kininogen
- LMX kininogen → produces kallidin
- HMW kininogen → produces Bradykinin


CPM/N
LMW kininogen
Kallidin
des – arg – kallidin
Aminopeptidase (AP)
(AP)
CPM/N
HMW kininogen
Bradykinin
(Action form)
des – arg – Brady kinin
(most active part)
Kallidin
des – arg – kallidin
B2
B1
Na^{+2}/ H_2O excretion
Vasodilation
Pain
Cough

DOC TUTORIALS
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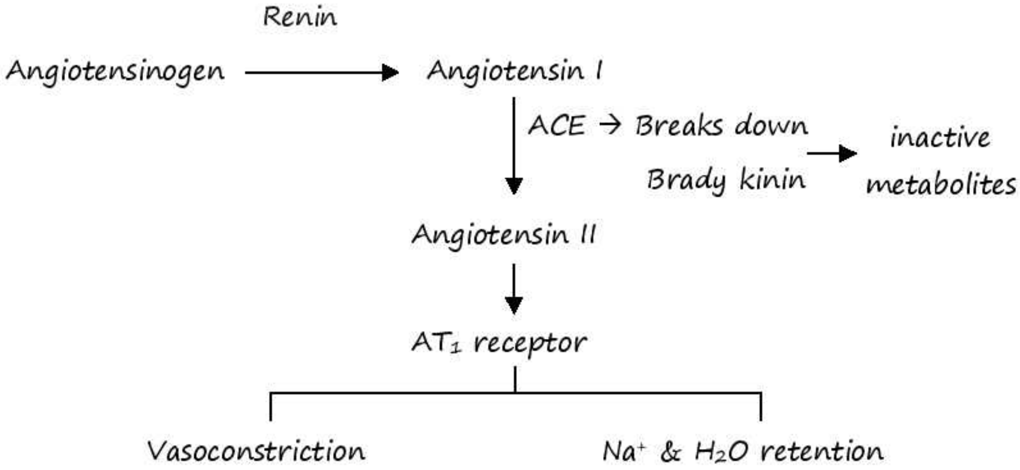
Renin
Angiotensinogen
Angiotensin I
ACE → Breaks down
Brady kinin
inactive
metabolites
Angiotensin II
AT_1 receptor
Vasoconstriction
Na^+ & H_2O retention

Carboxypeptidase M/N (CPM/N)	ACE
Breaks down bradykinin to active metabolite	Breaks down bradykinin
Kininase I	Kininase II
	Peptidyl – Di – peptidase enzyme

2.Renin inhibitors → 'Kiren' drugs
3.ACE inhibitors → 'Pril' drugs
4.Angiotensin receptor blockers → 'Sartan' drugs

Determinant	ACE inhibitors	ARB's	Renin inhibitors
Increase the levels of →	Angiotensin I Bradykinin	Angiotensin II → rapidly broken down by angiotensinase enzyme	Angiotensinogen
Decrease the levels of →	Angiotensin II Aldosterone	Aldosterone	Angiotensin I Angiotensin II
Hyper kalemia	Yes	Yes	Yes

Renal damage	Yes	Yes	Yes
Pregnancy	CI	CI	CI
Cough	Yes	No	No
CCF	Yes	Yes	Yes
Shortest acting	Captopril (least potent drug) Less absorption with food	Eprosartan	–
Longest acting	Perindopril	Telmisartan	–

Key points

- Cough – dry (30% incidence rate)
  - Prevention → Aspirin, Iron supplements (inhibit eNOS → NOxide levels low)
- `Protects diabetic kidney → DOC: HTN with DM (perindopril)

↓

Delays progression of diabetic nephropathy

↓

2nd DOC – ARB

3rd DOC – CCB

- Renal damage → Rise in serum creatinine (30%) within 2-5 days of therapy. Stabilized within 2-3 weeks.
- Pro-drugs → all are prodrugs except
  - Lisinopril (active)
  - Captopril (active)
- Postural hypotension → in sodium depleted individuals/ in Hypovolemic individuals.
- Enalapril → given by IV
- Serve angioedema & contraindicated in B/L renal artery stenosis
- Anti-hypertensive + calcium channel blockers →
  - Nifedipine
  - Amlodipine
- ACE inhibitors + ARB → Hyperkalemia (profound) hence the combination is contraindicated → but is indicated in! (Heart Failure and CKD with proteinuria. Decreases CVS morbidity when compared to Act – inhibitor monotherapy)

ARB

- Losartan →
  - Competitive antagonist of T_XA_2 receptors
  - Hence, additional antiplatelet activity is present (more than Irbesartan)

- Telmisartan →
  - Additional PPAR – gamma against
  - (PPAR-alpha → all fat → used in Hyperlipidemia → finrates
  - (PPAR-gamma → Glucose → used in Hyperemia → Thiazolidinedione's)
  - (PPAR-alpha + PPAR-gamma activity against → saroglitazar → can be used in DM with hyperlipidemia)

Drug of choice

- HTN with CM/CKD → ACE inhibitors (perindopril)
- HTN with angina → Beta-blockers
- HTN with BPH → Prazocin (tramsulosin is the DOC in BPH without HTN)
- HTN with pregnancy → labetalol

OSMOTIC DIURETICS

What is a diuretic?

- It is a substance that increases the urine output. → Increase Na^+ & H_2O excretion from body
- It is used especially when there is fluid over load within the body.
- Fluid overload is seen in CCF, Renal failure, liver failure, pedal oedema, ascites, pulmonary oedema.
- In such cases we need to let out fluid from the body so that patient can survive.

Osmotic diuretics 00:01:30

Where do the osmotic diuretics act?

- The most important area they act on are the Proximal convoluted tubule and descending limb of loop of Henle.

Drugs included in Osmotic Diuretics classification

- Mannitol
- Urea
- Glycerine
- Isosorbide

What is the mechanism of action of Osmotic diuretics?

- osmotic diuretic can be administered per orally or parenterally (most common routes) and gains entry into blood
- From the blood it moves into the urine, it is secreted out via the glomerulus and gains entry into urine.
- Now the osmotic diuretic agents are present in the lumen.
- The urine also contains H2O which is normally reabsorbed into the blood but this does not happen when we administer an osmotic diuretic.
- The osmotic diuretic behaves as a sponge, it absorbs all the water from the peripheral area (oedema) and takes it within the blood. Now these osmotic diuretics will take up the water and gain entry into the urine and not allow reabsorption of water. The water remains within the urinary tract (Lumen) and is excreted out from the body.
- The most important drug we have is mannitol,
- Mannitol prevents the reabsorption of water and decreases the plasma volume.

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Ions excreted out along with water by action of osmotic diuretics?

- Sodium (Na+), potassium (K+)
- Calcium (Ca2+), magnesium (Mg2+)

- Chloride (Cl–), bicarbonate (HCO3–)
- Water (H2O)

Pharmacokinetic Features

- Mannitol and Glycerine – both these drugs are given only by parenteral route iv.
- Isosorbide and urea – can be given by Per Oral route.

Uses of Osmotic diuretics

- Used in patients suffering from Oliguria
- Patients with increased Intra cranial tension or increased intra ocular pressure
- Drug induced Adverse drug reaction

Adverse effects of Osmotic diuretics

- Initial hyponatremia followed by hypernatremia due to compensatory mechanisms
- These drugs are contraindicated in cases of:
  1. Acute renal failure – kidney must be functioning normally in order to excrete the drug if the drug is prevented from excretion the drug accumulates in the body which further increases fluid volume.
  2. Cerebral hemorrhage – the drug must remain within the blood vessel if it is leaked out from blood vessel, that particular spot takes up all the

fluid and fluid accumulate in that area causing more pressure. Hence it is contraindicated.

3.Congestive cardiac failure

- Salient Features of Osmotic diuretics:
  - It cannot cross Blood brain barrier
  - It is freely filtered in the glomerulus.

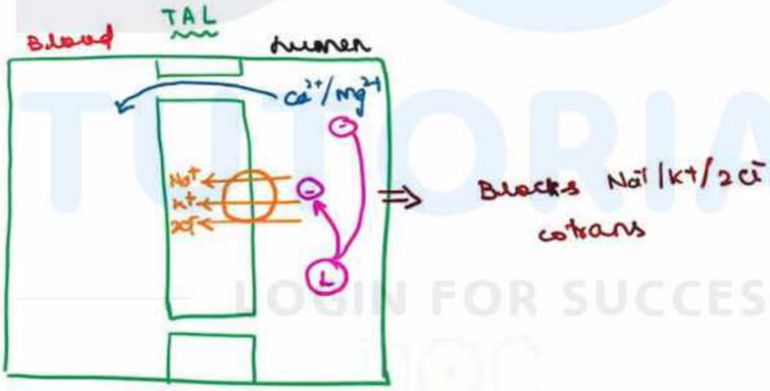
Loop Diuretics 00:11:36

Loop Diuretics (A.K.A High Ceiling and High Efficacy Diuretics)

- Acts at the loop of Henle (thick ascending limb)

1.Drugs—furosemide, bumetanide, ethacrynic acid, Torsemide.

2.MOA—



- Acts at the Na+-- k+-- 2cl- co- transporter.
- Ca2+ and Mg2+ transporter.

3.Uses - cerebral edema

- Acute pulmonary edema.

4.Excretes—Na+, K+, Cl-, Ca+2, Mg+2, H2O.

5.PK—good PO availability—60 to 90%

- DOA—6 hrs. (LASIX)

- Secreted into the PCT.

6.Adverse reactions—

- Hyponatremia
- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Hypovolemia or dehydration
- Hyperuricemia
- Hyperglycemia
- Metabolic alkalosis (does not excrete HCO_3)
- Ototoxicity (always slow IV)
- Increase LDL and decreases HDL levels.

7.Salient features--

- Ethacrynic acid → most ototoxic
- Torsemide → long $T_{1/2}$
- NSAIDS attenuate loop diuretics effect
- Drug of choice in moderate to severe RF.
- Additional Vasodilatory action.

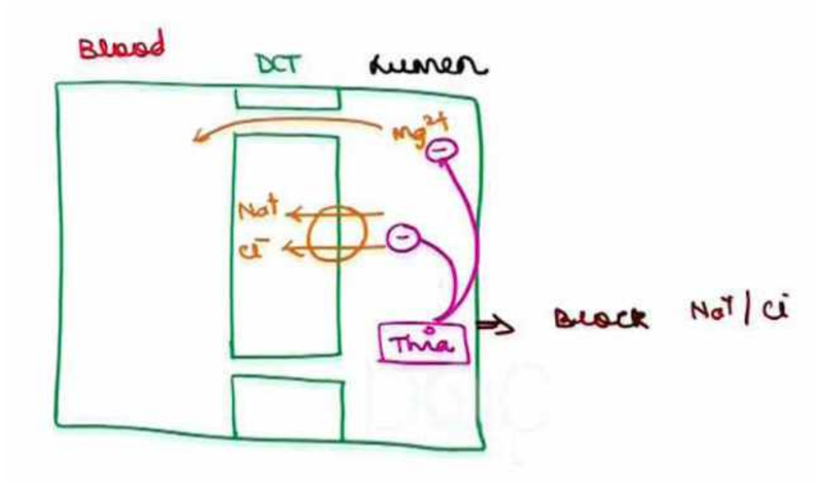
Thiazide Diuretics 00:20:39

- Act on DCT

Drugs

- Thiazide diuretics.
- Thiazide like diuretics—indapamide, metolazone, chlorthalidone

MOA:



- Sodium chloride symporter is blocked by thiazides.
- Magnesium reabsorption is inhibited too.
- Hence, the following ions are excreted—Na^+, K^+, Cl^-, H_2O, Mg^{+2}
- On long term administration, Ca^{+2} also is excreted.

Uses:

- Main faience therapy for hyper tension.
- Mild to moderate CCF
- Nephrogenic DI
- Hypercalciuria
- Nephrolithiasis

Adverse effects:

- Hyponatremia
- Hypokalemia
- Hypomagnesemia
- Hypovolemia
- Hypercalcemia
- Hyperuricemia

- Hyperglycemia
- Others like—metabolic alkalosis, erectile dysfunction, increases LDL and triglycerides.

Salient features:

- Medium efficacy diuretics.
- Decrease the GFR—hence CI in acute renal failure except metolazone and indapamide.
- Additional carbonic anhydrase inhibitory property.
- More efficacious than the loop diuretics in treating hypertension. (chlorthalidone)
- Diuretics + ACE inhibitors. → combination produces postural hypotension—prevented by decreasing the dose of diuretics.
- Diuretics and ACE inhibitors decrease and increase potassium respectively and hence they cancel out.

POTASSIUM SPARING DIURETICS

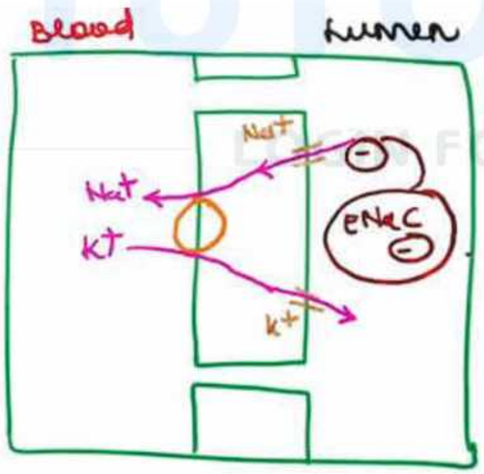
- Date of action DCT & collecting duct.
- Drugs:

Epithelial Na channel ⊖	Aldosterone ⊖
Amiloride	spironolactone
Triamterene	Canrenone
	Eplinerone.

- Weak Diuretics

MOA

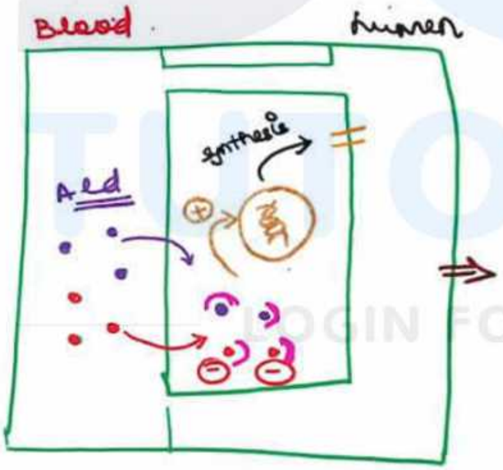
- Cause excretion of Na^+ and water, spare the excretion of K^+.
- Do not cause hypokalemia.
- Cause hyperkalemia if combined with ACE inhibitors so their combination is not generally prescribed.



- Epithelial Na channel ⊖
- K^+ is not excreted out.

- Na^+ is excreted out.
- Ameloride → most potent –
  - Used for lithium induced polyuria.
  - Cystic fibrosis.
  - Liddle syndrome.
- Triamterene → causes –
  - Megaloblastic anemia.
  - Inters trial nephritis.
  - Nephrolithiasis.
- So amiloride is preferred over triamterene.

Aldosterone ⊖



- Aldosterone binds with its receptor.

  ↓

  Increases synthesis of Na^+ channels for reabsorption.

Spironolactone binds aldosterone receptor and inhibits synthesis of ENAC.

↓

Only drug acting from blood site.

- Spironolactone $\xrightarrow{active}$ canrenone

↓

Diuretic action

Adverse effects

1. Gynecomastia – maximum with spironolactone.
   Minimum with eplerenone.
2. Impotence.
3. Hyperkalemia.
4. Prone to DI.

Uses

1. Combined with Loop & thiazide to space 'K' excretion
2. Weak diuretics.
3. In CCF.
4. In HTN
5. In cirrhotic edema.
6. Hirsutism.

Carbonic Anhydrase Inhibitors 00:12:00

Act at the PCT and DCT.

1. Drugs—acetazolamide, brinzolamide, dorzolamide.
2. MOA –
   - Transport of Na+ from the blood into the PCT and DCT occurs in exchange with H+ ions.

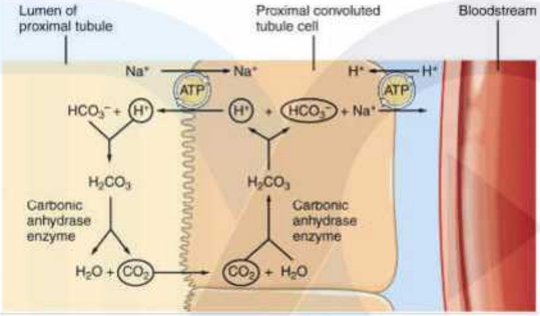

Lumen of proximal tubule
Proximal convoluted tubule cell
Bloodstream
Na^+
Na^+
H^+
H^+
ATP
ATP
$HCO_3^- + H^+$
$H^+ + HCO_3^- + Na^+$
H_2CO_3
H_2CO_3
Carbonic anhydrase enzyme
Carbonic anhydrase enzyme
$H_2O + CO_2$
$CO_2 + H_2O$

Fig: 1

   - H+ combines with HCO3– to form H2CO3 which in turn splits to H2O and CO2 by carbonic anhydrase type 2 (both water and CO_2 produced are penetrable).
   - CA2 enzyme is blocked by CA enzyme itself which acts as a noncompetitive reversible blocker.
   - H_2o and CO_2 after entering the PCT and DCT, combine to form H2CO3. H2CO3 again breaks down to H+ and HCO3–.
3. Increases the excretion of—
   - Sodium
   - Potassium

- Bicarbonate
- Water

4.Uses--

- Glaucoma—as it decreases aqueous humor.
- Seizures—increases CO2 in brain, decrease in PH
- To alkalinize urine
- Mountain sickness
- Periodic paralysis.

5.Adverse reaction-

- Metabolic acidosis (increased in COPD)
- Hypokalemia
- Drowsiness
- Hypersensitivity
- Bone marrow suppression
- Contraindicated in liver pathologies.

6.Salient features ---

- At high doses, it decreases gastric acid and pancreatic NaHCO3 secretions
- Sulfonamide derivatives—hence similar side effects to the parent drug
- Maximum kaliuretic (excretion of potassium) when compared to other diuretics.
- Diuretics → Weak in action

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DRUGS FOR CONGESTIVE CARDIAC FAILURE

PART - I

Congestive cardiac failure 00:00:12

- **Question:** what is congestive cardiac failure?

- **Answer:** whenever the **heart is unable to supply enough amount of blood or supply oxygen to individual parts of the body due to decreased ventricular function.**

Decreased left ventricular function

↓

Decreased cardiac output which
decreases the blood supply to brain.

↓

Activates the compensatory mechanism
to increase the blood volume.

↓

Activates neurohumoral process that is:
sympathetic autonomic nervous system (SANS)

&

Renin angiotensin aldosterone
system stimulated (RAAS)

↓

Due to which sodium & water retention mechanism
begins.

↓

Blood volume increases

↓

Due to renin angiotensin mechanism there will be vaso-constriction

↓

Venous return increases

↓

Already the heart is unable to pump out blood due to increases load on heart

↓

Further decreases left ventricular function.

Treatment - acute decompensated failure -

00:02:44

i. Symptomatic relief → **diuretics** (furosemide & bumetanide).

ii. **Positive ionotropic effect** (force of ventricular contraction)

- Dobutamine
- Dopamine
- Enoximone (iv)
- Levosimendan

iii. Vasodilatation -

- To decreases the load on heart drugs used are: nitrates, nitroprusside, Nesiritide.

- Positive ionotropic drugs and vasodilators are called.

Ionodilators:

i. Milrinone

ii. Vesnarinone

iii. amrinone

Disease modifying agents 00:05:18

- Drugs which are going to decrease the mortality –
  - M – Mortality/reducing remodeling of heart.
  - I– ivabradine.
  - S – spironolactone/sacubitril + valsartan.
  - B – beta – blockers.
  - A – ACE inhibitors/ARB'S (renin inhibitors not used)
  - H– Hydralazine + ISDN.

- **Question**: why hydralazine 7 ISDN given in combination?
- **Answer:**

i. Hydralazine decreases tolerance of nitrate to develop.

ii. BIDIL (Bi-dilator agent) hydralazine is an arteriolar dilator, while ISDN is a venodilator.

- It dilates both arteries and veins at the same manner.

Positive ionotropic drug:

- **Digoxin**, not used in acute therapy used as disease modifying or last mode of therapy in treatment.

Treatment of acute CHF with systolic dysfunction

00:07:50

- Drug of choice –
  - **Dobutamine**: it has 2 different isomers it has got negative isomer and **positive isomers**.
  - **Negative isomer** → acts as **agonist of alpha2 agent** and also as weak $beta_1$ & $beta_2$ agonistic agent.
  - **Positive isomer** → acts as $beta_1$ & $beta_2$ **agonistic agent** and weak $alpha_2$ agonistic agent.
  - **The mixture is given in the treatment of congestive cardiac failure.**
  - Dobutamine has **advantages over adrenaline like**:
    i. Causes less tachycardia than adrenaline.
    ii. Decreases pulmonary wedge pressure.

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Natriuretic peptide analogues: 00:09:53

- There are 3 types of analogues

  1.ANP

  2.BNP

  3.CNP

- It increases the excretion of sodium from the body as sodium is getting excreted water is also getting excreted → blood volume decreases→ bad on heart also decreases thereby increase the survival of the patient.
- Maturation of these drugs are short acting because they are peptides it is broken down by peptidase enzyme as it is short acting analogue cannot be used for chorine therapy it has been implied for only acute congestive cardiac failure.

Atrial NP	Brain NP	CNP
Act on NPRA (Natriuretic peptide receptor-A) (most important)		↓ Natriuretic peptide receptor-B (NPRB)

- It gets secreted out from the cardiac muscle when there is increase in blood volume or whenever there is increase in the ventricular contracting force.

- NPRA is seen on the cell wall it is a transmembrane receptor/membrane linked receptor.
- **Transmembrane receptor is linked with activation of endogenous guanyl cyclase receptor.**
- Because of its binding guanyl cyclase is activated which converts GTP to CGMP.
- This cyclic GMP is going to be in turn is responsible for 3 major functions:

  1.Natriuretic

  2.Diuresis

  3.Vaso dilation because of nitric oxide.
- As natriuretic peptide gets broken down by peptidase enzyme which is neutral endo peptidase enzyme (NEP) also called as **NEPRILYRIN**.
- The half-life of heretic peptide gets shorter.

  1.Drugs of ANP analogues:

    - Urodilantin carper tide.

  2.Urodilantin analogues drugs:

    - Ularitide.

  3.BNP analogues drug:

    - Neseritide very short acting drugs should be given parenterally as it is broken down by peptidase enzyme.

  4.NEP inhibitors

    - Ends with trills

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- Sacubitril → used in treatment of congestive.
- Racecadotril → cardiac failure given with valsartan.

↓

Used in treatment of secretory diarrhea (inhibitors enkephalinase)

↓

(Increases encephalin (opioid) (causes constipation)

↓

(Used secretory diarrhea)

Nersritide:

- Increases CGMP (as it is peptide).
- It causes vasodilatation which is similar to glycerin trinitrate).
- Rapidly metabolized by NEP (t1/2 20 minutes)
- It has four classical features:

1.Given via injection (due to shorter acting).

2.No value in chronic failure

3.No oral absorption

4.Adverse effect: **Nephrotoxicity and Hypotension**

5.Currently approved for relieving dyspnea in acute refractory decompensated congestive cardiac failure (CCF).

DRUG FOR CONGESTIVE CARDIAL FAILURE PART - II

ACE inhibitors 00:00:04

- ACE inhibitors → tril drugs
- NEP inhibitors → tril drugs

  (Neutral endo peptidase)

ACE inhibitors 00:01:05

- ACE + NEP inhibitors → trilat drugs

  ↓ Causes vasodilatation.

  ↓ also called as Vaso peptidase inhibitors
- Inhibition of ACE causes accumulation of bradykinins

  Increase bradykinin → increase vasodilatation
- Inhibition of NEP causes increase natriuretic peptides leading to vasodilatation
- ACE also called as "Peptidyl di peptidase" enzyme

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- Trilat drugs → omapatrilat

  Sumapatrilat

  } Increase risk of angio edema more than ACE inhibitors monotherapy

Inodilators 00:00:04

INO DILATOR → vaso or veno dilators

↓

Positive inotropic

Positive inotropic

↓

Cardiac muscle (CM) contraction

Vaso dilation

↓

smooth muscle (SM) relaxation

↓

Inhibited by P Δ E -3 (CM+SM)

Milrinone, enaminone, vesnarinone

- Milrinone – increase mortality on chronic use due to development of thrombocytopenia
- Thrombocytopenia [inamrinone > Milrinone]
- Indication for milrinone → right sided acute HF with pulmonary hypertension as milrinone decreases mortality and has additional smooth muscle relaxation activity

Cardia glycosides 00:05:42

Cardiac glycoside drugs are –

1. Digoxin
2. Digitonin
3. Strophanthine
4. Oubain
5. Lama to side C

MOA

i. Vago mimetic activity [treatment – Atrial Fibrillation]

ii. Noncompetitive, irreversible inhibition of Na^+/K^+ ATPase Pump [treatment: Congestive cardiac failure]

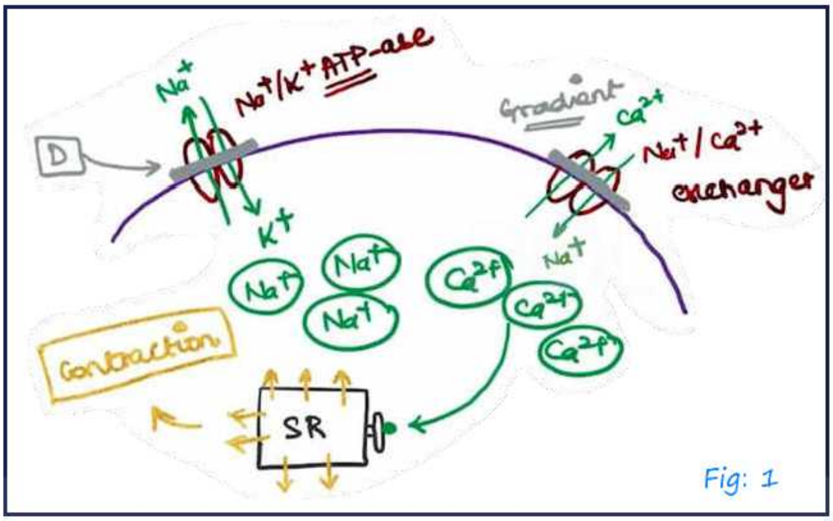
Na^+
Na^+/K^+ ATP-ase
D
K^+
Gradient
Ca^{2+}
Na^+/Ca^{2+} exchanger
Na^+
Na^+
Na^+
Na^+
Ca^{2+}
Ca^{2+}
Ca^{2+}
Contraction
SR

Fig: 1

- Active transport against gradient tatus place as there is Na^+ efflux and k^+ influx
- Digoxin blocks the Na^+/K^+ ATPase pump NC-IR blockade; dosage dependent
- Binds to allosteric site because of which Na^+ ions do not leave the cell
- Cell must be in depolarized state to accumulate mere Na^+ ions to achieve contraction
- Na^+/Ca^{+2} exchanger pump
  Normal function → influx of Na^+ and efflux of Ca^{+2}
  Gradient blocks Na^+ influx and Ca^{+2} efflux causing increase Ca^{+2} accumulation within the cell.
- Accumulated Ca^{+2} causes calcium – induced calcium release from sarcoplasmic reticulum Ca^{+2} binds to Ryanodine receptor (RYR) on surface of SR and release of stored Ca^{+2} from SR → contraction of cardiac cells

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Key points about digoxin 00:12:28

1. Does not increase oxygen consumption of cardiac muscle
2. Very high volume of distribution (VD) ≈ 6L/kg
   Hence, dialysis cannot be used in a patient of digoxin poisoning as because of its high Vd, more amount od drug is stored in the periphery and cells; less amount of drug in blood.
3. Absorption of drug decreased by normal get flora – Eubacterium lantum
4. Has narrow therapeutic lenders. Concentration of drug to be maintained between 0.5-0.8 ng/ml.
   >1.2ng/ml → increases mortality
5. 25% plasma protein bound t1/2 – 40 hours
6. Predominant reservoir → skeletal muscles
7. Contra indications
   i. Hypertrophic obstructive cardiomyopathy
   ii. High output failure
   iii. Acute rheumatic carditis
   iv. Wolf Parkinson white syndrome
   v. Thyrotoxicosis
8. Structure
   - Cardenolide → positive inotropic effect
   - Glycoside → pharmacokinetic effects of digoxin

Digoxin – Adverse drug reactions 00:17:00

- Non cardiac
  - Nausea, vomiting (most common)
  - Anorexia (earliest drug reaction)
  - Xanthopsia (Yellow vision)
  - Gynecomastia
  - Hyperkalemia
- Cardiac
  - Arrhythmia – most common: pre ventricular beats, ventricular bigeminy
- Characteristic
  - Paroxysmal atrial tachycardia (or) non-PSVT with variable heart block
  - It will never cause scuff these two conditions
    1) Atrial flutter
    2) Mobitz type II

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Factors that increase toxicity

- Decrease K^+ - increase digoxin toxicity
- Decrease Mg^{+2} – increase digoxin toxicity
- Increase Ca^{+2} – increase digoxin toxicity
- Renal failure, increase digoxin toxicity

Digoxin electrical changes 00:20:35

1. Effective refractory period
   - Increase in AV node

- Decrease in atrium and ventricles

2. Conduction velocity
   - Decrease in AV node
   - Increase inn atrium
   - No effect in ventricles
3. Automaticity → increase in all three
4. Increase in AV refractory period → PR prolongation
5. Increase in ventricular contraction → shortened ST interval accelerated repolarization of inner myocardium causing inverted T waves

Toxicity 00:23:35

1. Mild → KCL infusion can be used
2. Acute → Digi bind [depends on plasma concentration of digoxin]

Treatment:

- Brady cardia – atropine
- Tachycardia – potassium
- SVT – propranolol
- VT – lignocaine/phenytoin

No use in acute poisoning -

1. Dialysis → high
2. Cardio version → increases mortality
3. K^+ → already hyperkalemia

Drug interactions 00:25:55

1. Cholestyramine → decrease absorption of digoxin
2. Thiazide → hypokalemia causes increase digoxin toxicity
3. Quinidine –
   1. Decreases binding of digoxin to plasma protein, increase free drug leading to increased toxicity
   2. Decreases excretion of digoxin as it inhibits P-glycoprotein

Levosimandan 00:27:38

- Blocks P → Blocks PΔE-3
- Opens P → opens potassium channels
- Binds P → Binds to trop-c and sensitizes myocardium to calcium.

Never drugs-

1. Lsteraoxime
2. Omecantio mecarbil

ANTI-ARRHYTHMIC DRUGS-I

Anti-arrhythmic drugs 00:00:10

- In pacemaker cells, there is no true resting membrane potential but there is a threshold potential.
- When the cell reaches threshold potential, there is influx of Ca^{+2}.
- After threshold at peak and cell becomes more positive K^+ ions keep coming out now the membrane change keeps getting less positive.
- Na+ channels open (slow Na+ channel)→hyperpolarization –activated – cyclic-nucleotide-gated-Na^+ channels.
- Slow Na^+ channels allow the cell to regain its normal threshold potential.
- This is followed again by influx of Ca^{+2} & efflux of potassium (K^+)

Conducting cell 00:05:25

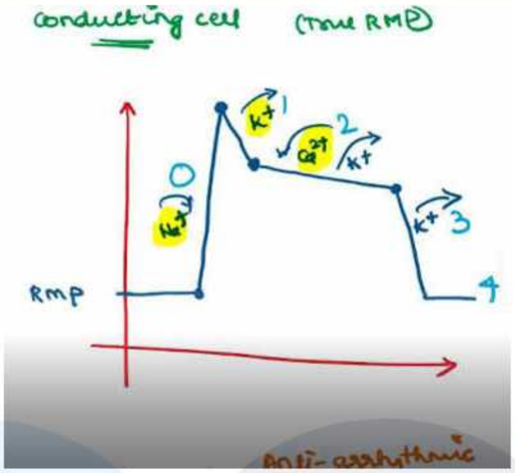
conducting cell
(True RMP)
0
Na+
K+
1
Ca2+
2
K+
K+
3
4
RMP
Anti-arrhythmic

Fig: 1

- Action potential in a conducting cell.
- A true resting membrane potential is present.
- Rapid Na^+ influx increases positive charge of the cell.
- Now k^+ is pumped out (too much positive charge in the cell) the cell becomes less positive.
- Calcium influx and potassium efflux occurs in between.
- Finally, K^+ efflux occurs and the cell reaches RMP.
- Different ions responsible for action potential:

  i. Na^+

  ii. K^+

  iii. Ca^{+2}

Anti- arrhythmic classification 00:07:35

Na	Bi's	Proto	Col
↓	↓	↓	↓
I	II	III	IV
↓	↓	↓	↓
Na^+ channel blockers	β-blocker	K^+ channel blocker	Ca^{+2} channel blocker

- Arrhythmic
  - i. Supra ventricular arrhythmic
  - ii. Ventricular arrhythmic
- Primary ion that is responsible for action potential in the atrium → Ca^{+2} → blocked in treatment of supraventricular arrhythmia
- Primary ion that in responsible for action potential at the conduction sites → Na^+ → blocked in treatment of ventricular arrhythmic.
- A newer drug called **ADENOSINE** which is **K+ channel opener** is used now

Sodium channel blocker: type I anti-arrhythmic

00:09:58

Sodium channel blocker: Type I anti-arrhythmic

Ia (1-10sec)
↓
Block "open Na⁺ channels + K⁺ channels
↓
Causes moderate phase 'O' depression
↓
Prolongs phase 3 (repolarization)
↓
Prolong action potential duration
↓
Ia
↓
QT prolongation

Ib(< 1sec)
↓
block inactivated Na⁺ channels + opens K⁺ channels
↓
weak phase 'O' depression
↓
shortens phase 3 (repolarization)
↓
shortens/no effect on APD
↓
Ib
↓
QT shortening

Ic (>10sec)
(most potent)
(Most proarrythmogenic)
↓
block open Na⁺ channels + no action on K⁺ Channels
↓
marked phase 'O' depression
↓
no effect on phase 3
↓
prolongs APD
↓
Ic
↓
no effect on QT

Class – I a drug:

- Quinidine:
  - Na$^+$ & K$^+$ channel blockage.
  - Vagolytic.
  - In high doses, Ca^{+2} channel blockade.

Quinidine properties

Cardiac properties	Non-cardiac muscles
i. Decrease automaticity (especially ectopic pacemaker cells) No effect on SA mode.	i. Decrease blood pressure (weak alpha blockade property)
ii. Slows the conduction velocity	ii. Decreases skeletal muscle contraction.
iii. Refractory (RP) period → inertia → marked increase. In ventricles → mild increase Av node → increase RP (direct). Decrease Rp (vagolytic)	iii. Anti-malarial.
	iv. Anti-pyretic
	v. Weak – oxytocic property

Adverse drug reactions:

i. Bradycardia/CCF
ii. Torsade's – de- pointes (TDP)
iii. Hypotension in elderly
iv. Embolic phenomenon
v. Hypersensitivity reactions
vi. GIT → nausea, vomiting, diarrhea
vii. CNS→ headache, seizures
viii. Cinchonism

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Contraindications of quinidine:

1. Preexistent conditions (drugs causing QT prolongation→ because quinine causes TDP esp. in hypokalemia.
2. Stokes – Adams.
3. **Ventricular tachycardia with AV block**
4. Myasthenia.
5. **Digoxin induced arrhythmia.**

Procainamide 00:22:29

- Amide derivative of procaine.
- Very similar to quinidine.
- No CNS toxicity.
- Less suppression of automaticity.
- **No vagolytic effect.**

- No alpha – blockade.
- No cardiac depressant property.
- Metabolized by acetylation.
  1. Sulfonamides
  2. Hydralazine
  3. Isoniazid
  4. Procainamide
  5. Dapsone
  6. Clonazepam

Adverse effects:

1. Hypersensitivity reactions
2. TDP
3. IV route → hypotension
4. GI reactions
5. Agranulocytosis and SLE (hence not prescribed for more than 6 months).

Disopyramide 00:25:50

- Na^+ channel blocker (open stage Na+)
- Anticholinergic
- No alpha-blockade side effects.
- If it acts directly → it decreases heart rate.
- Because of the anticholinergic property → it increases the heart rate.
- Contraindicated in prostatic hypertrophy.

ANTI ARRHYTHMIC DRUGS – II

Class IB – Lignocaine 00:00:10

- **Only IV route other parenteral routes for S.C will have** local anesthetic action
- **IV only with adrenaline combination**
- I.M → Rarely given
- P.O → Good absorption, high FPM (dependent on hepatic blood flow)
- Hence, **drugs decreasing the hepatic blood flow will increase the bioavailability of lignocaine**

Actions

1. Suppresses automaticity (ectopic foci) → Pathology selective (Safe)
2. **Rapid onset & short duration of action. (Hence, cannot be given in chronic condition)**
3. Toxic effects (In case of overdose) last for a short while
4. **Least proarrhythmogenic as it is a K^+ channel opener**
5. No effect on conduction velocity → D.O.C for digoxin induced arrhythmia
6. No change in electrophysiology of atrium/SA node/AV node when lidocaine is administered. Hence it cannot be used in atrial arrhythmia

7. D.O.C for Ventricular tachycardia & Ventricular tachycardia following MI
8. Causes drowsiness, and rarely conclusions IV diazepam must be kept ready
9. Avoided in liver failure as it is metabolized by the liver enzymes
10. Cimetidine and propranolol decrease hepatic blood flow

Tocainide

- Neurological Adverse reactions

Mexiletine

- Given via P.O
- Is a lignocaine analogue
- No first pass metabolism

Class IC 00:07:05

Flecainide

- P.O or slow IV
- Flecainide = Fluorinated procainamide
- Uses
- PSVT
- VT
- WPW syndrome
- Prolongs PR interval, QRS & QT (least)

- Tendency to cause arrhythmia & sudden cardiac death
- MC adverse effect→ Blurred vision
- Flecainide increases mortality post MI

Propafenone 00:09:10

- Mild beta blockade property
- **Mild Ca^{+2} channel blockade**
- Causes bradycardia & bronchospasm
- **Prolongs PR interval, QRS and sinoatrial node**
- Adverse Effects
- CCF
- Dyspepsia
- Dysgeusia
- Propafenone is metabolized by CYP2D6

Metabolized by CYP2D6

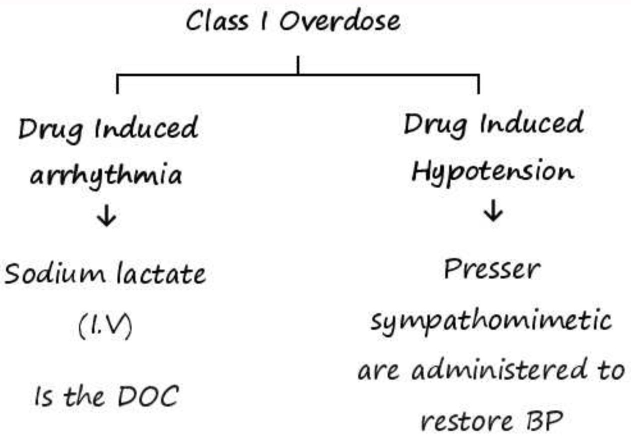
- Metoprolol
- Celiprolol
- Propafenone

Moricizine

- Longt1/2

Encainide

Class I overdose 00:11:28



Class I Overdose

Drug Induced arrhythmia
↓
Sodium lactate (I.V) Is the DOC

Drug Induced Hypotension
↓
Presser sympathomimetic are administered to restore BP

Class II antiarrhythmics 00:12:41

Beta blockers

- Prolong refractoriness in AV node
- Has membrane stabilizing property
- As they decrease contractility, the oxygen demand of cardiac muscle also decreases
- Used in the treatment of sinus tachycardia & SVT (Especially if precipitated by exercise, emotions, thyrotoxicosis)
- Reduces all – cause – cardio vascular mortality
  - Propranolol
    i. Synergism with class I & III antiarrhythmic
    ii. Ci with class IV (CCB) – Serious conduction abnormalities are caused

Class III K^+ Channel Blockers 00:15:09

Sotalol

- Class III drug with additional class II activity
- P.O/I. V route
- No membrane Stabilizing action
- No negative ionotropic effect
- Pro arrythmogenic potential
- Given as a racemic mixture

Amiodarone 00:16:41

- Contains iodine
- Structure similar to thyroxine
- Propensity to cause hyperthyroidism – wolf chaikoff effect
- Broad spectrum antiarrhythmics (Na^+ B + β –B + K^+CB^{++} + CCB +α Blockade)
- Slows conduction on AV node
- Decreases automaticity of SA node, Atria and AV node
- Decreases blood pressure through calcium channel blockade and alpha blockade
- Decreases HR because of beta-blockade
- Ultra-long-acting agent as it has high volume of distribution (18-60 days)
- Amiodarone increases cardiac output (even if it blocks beta & Ca^{+2} receptors)

- Slow onset of action (rarely used for acute conditions)
- Embryo toxic drug

Adverse drug reactions

- **Most common→ GI related followed by next most common → Photosensitivity**
- N→ Neurotoxicity (Peripheral neuropathy & proximal muscle weakness)
- I → High Vd, spectrum, duration
- **L → Lungs (pulmonary fibrosis if dose is > 400mg/day)**
- E → Eye (Asymptomatic corneal micro deposits)
- **S → Smurf skin**
- H → Hepatotoxicity (Causes pseudo alcoholic liver injury)
- **Hypothyroidism → Hyperthyroidism**
- **Hypotension (Because of the alpha blockade) Heart (myocarditis)**

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Dronedarone 00:23:13

- **Lacks iodine**
- Does not cause thyroid dysfunction
- Does not cause pulmonary fibrosis
- Less efficacious

Causes

- **Bradycardia & QT prolongation**
- Propensity to cause hepatotoxicity
- Increased creatinine levels
- More anti-adrenergic adverse effects than amiodarone

Ibutilide 00:25:00

- Similar to amiodarone
- Given by IV route
- K^+ channel blockade + Na^+ channel opener (Opposite to lidocaine)

Dofetilide

- Given via P.O route
- Over 80% is excreted unchanged in urine

Vernakalant

- Parenteral route
- **Block ultra-rapid delayed rectifier K^+ channels in atria**
- **Also block sodium channels and muscarinic receptors operated K^+ channel blockers**
- Vernakalant can be used for rapid conversion of A-fib (< 7days duration) to normal sinus rhythm
- **CI in hypotension, bradycardia**
- **Has no proarrhythmogenic potential**

ANTI-ARRHYTHMIC DRUGS - III

Class IV anti-arrhythmic drugs 00:00:08

- Verapamil
- Diltiazem
  - **Verapamil and diltiazem are preferred over dihydropyridines like Amlodipine because they have more cardiac effect and less vascular effect.**
  - Dihydropyridines are also not preferred because they cause vasodilation on which decrease BP and in turn there is reflex tachycardia.
  - Verapamil is **contraindicated with β- blockers, Quinidine and disopyramide because they cause negative ionotropy.**
  - Mechanism of action of Verapamil: -
- Inhibits Ca^{+2} medicated depolarisation
- No change in intraventricular condition

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Diltiazem

- **Less negative ionotropic effect**
- Direct cardiac action
- **Negative ionotropy, chronotropy, dromotropy effect is more with verapamil.**
- Decrease in automaticity of SA and AV mode is equal in both verapamil and diltiazem
- Diltiazem is **preferred in rapid control of ventricular rate in Fibrillation**

Class V anti-arrhythmic drugs 00:04:15

- ADENOSINE
  - Purine nucleoside
  - Normally released post M.I
  - Mechanism of action
    1. Acts as A1 receptor against
    2. Open K^+ channels
    3. Decrease automaticity, decreased action potential duration.
    4. Since there is no fixed resting membrane potential for a pacemaker cell we can make it extremely hyperpolarised which results in decrease in heart rate.
- Adenosine is not used to treat ventricular tachycardia
- **Adenosine has short T1/2 because it is taken up and stored by RBC's**
- Given i.v infusion / i.v bolus followed by 20ml fluid push
- Preferred sites for administration
  - i. **Left arm cubital vein**
  - ii. **Central vein**
  - iii. **Intra- osseous vein**
- Adenosine has no negative ionotropy therefore it is safer than verapamil
  - i. Bronchial asthma
  - ii. Sick sinus syndrome

- Drug Interactions
  - i. Dipyridamole increases adenosine by blocking its reuptake by RBC's
  - ii. Theophylline decreases activity of adenosine by blocking A1 receptors
- In patients with wide QRS tachycardia adenosine is preferred over verapamil
- Uses
  - i. PSVT
  - ii. To induce brief coronary vasodilation
  - iii. To induce controlled hypotension

Other class V drugs

- Digoxin used I patients with low Left ventricular ejection fraction
- K^+ → prolongs refractory period in Purkinje fibres
- Mg^{2+} →
  - Given as slow injection
  - Drug of choice for TDP (Torsade's De Pointers)
  - Used as emergency treatment of ventricular tachycardia and digoxin induced arrhythmia
- Atropine
  - Anticholinergic agent
  - Drug of choice for Bradycardia or AV-block
  - Can only be used for arrhythmia and not CCF

HAEMATINICS

Drugs acting on blood components 00:04:12

Drugs which increase the level of

- RBC
- WBC
- Platelets

RBC
↓
Erythropoietin
↓
Darbepoetin α
↓
i. CKD
ii. BMD
Induced anemia

WBC

- G-CSF
  ↓
  Filgrastim
  Deg-filgrastin
- GM-SCF
  ↓
  Sargramostim

Leucopenia
(Anti-cancer)

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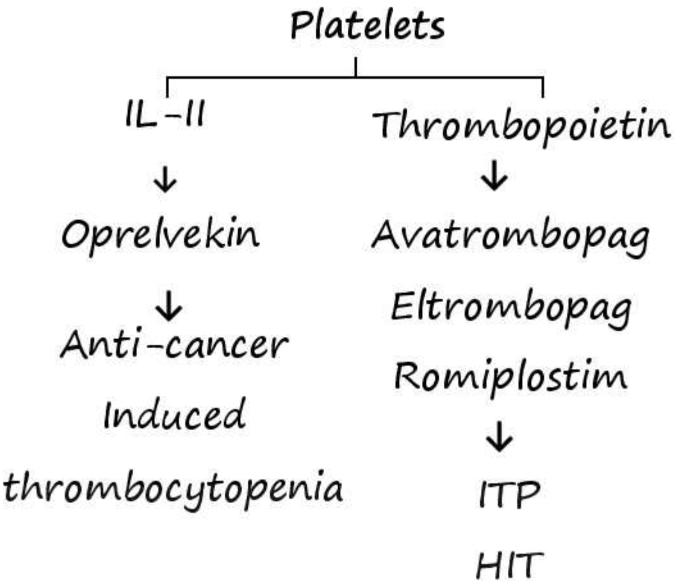
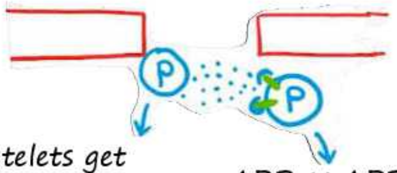

Platelets
IL-11
Thrombopoietin
Oprelvekin
Anti-cancer
Induced
thrombocytopenia
Avatrombopag
Eltrombopag
Romiplostim
ITP
HIT

ANTI-COAGULANTS

Platelet activation



Platelets get activated
↓
Releases ADP

ADP ↔ ADP-R
(Receptor)
↓
Activation of other platelets
↓
Platelet activation cascade

- Ⓟ - 1st platelet which comes in contact with VWF & collagen

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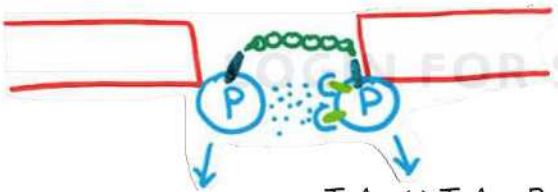
Platelet accumulation



Activated platelets
↓
Releases T_xA_2

$T_xA_2 \leftrightarrow T_xA_2$-R
(Receptor)
↓
Expression of GP II_b/III_a-R
↓
Interacts with fibrinogen $\xrightarrow[\text{factors}]{\text{Clotting}}$ Fibrin
↓
Inactive strands

Plasmin ← Plasminogen
⊕
tPA
↑ ⊕
fibrinolytics

Platelet activation & accumulation $\xleftarrow{\ominus}$ Anti-platelets

Anti-coagulants 00:08:56

1. Safe in pregnancy → **Heparin – both unfractionated < LMWH**
2. Heparin resistance – **Therapeutic aPTT not achieved even after giving >35,000 U of heparin per day**
3. Warfarin less effective in nephrotic – **due to albuminuria; warfarin – albumin bound**
4. LMWH advantageous than UFH – **more stable, long acting, less adverse effects**

Drugs

⊖ Thrombin generations

⊖ Thrombin activity

⊖ Clotting factors

↓ Indirect

UFH ($X_a=II_a$)

LMWH ($X_a \geq II_a$)

FONDAPARINUX ($X_a >> II_a$)

DANAPAROID

⊖ Zymogens

- Warfarin
- Acenocoumarin
- Phenindione (not used now nephrotoxic)

Danaparoid

Indirect

↓

⊕ Antithrombin (AT)

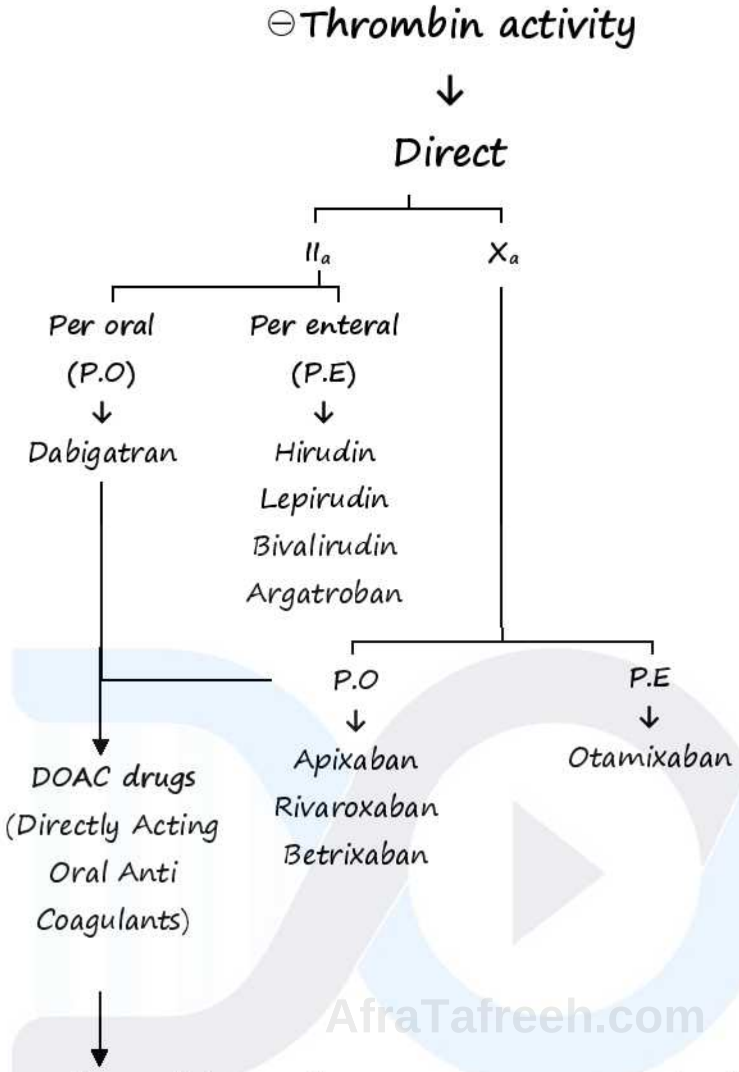
↓

$\ominus X_a$

Direct

↓

⊖ Thrombin activation of factor IX

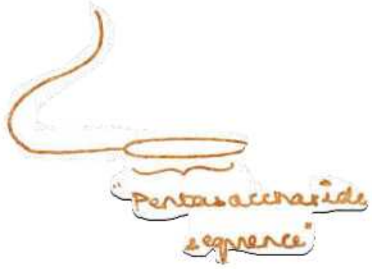

⊖Thrombin activity
Direct
II_a
X_a
Per oral (P.O)
Dabigatran
Per enteral (P.E)
Hirudin
Lepirudin
Bivalirudin
Argatroban
P.O
Apixaban
Rivaroxaban
Betrixaban
P.E
Otamixaban
DOAC drugs (Directly Acting Oral Anti Coagulants)

- Preferred in ortho surgery, non-valvular A.fib, pulmonary embolism
- Rivaroxaban → used in acute coronary syndrome

DOC TUTORIALS
LOGIN FOR SUCCESS

Indirect agents 00:17:45

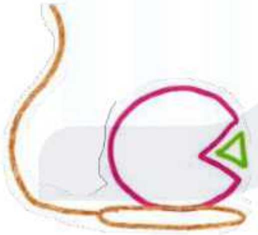
UFH


"Pentasaccharide sequence"

AT

X_a

II_a



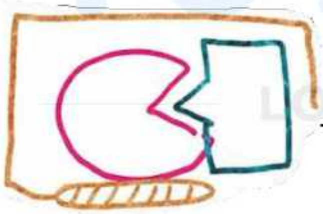
AT activated (1000-fold)

↓

Induces conformational change in X_a

↓

⊖ X_a



AT activated (1000-fold)

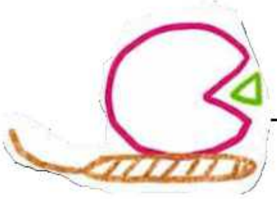
↓

Scaffolding & conformational change in II_a

↓

⊖ II_a

- LMWH – pharmacologically more stable



AT activated

↓

conformational change in X_a

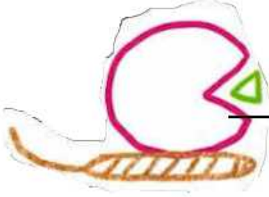
↓

⊖ X_a

↓

Minimal activity on II_a

Fondaparinux



AT activated

↓

conformational change in X_a

↓

⊖ X_a

↓

Minimal activity on II_a

- More anti-X_a activity than LMWH
- More t ½ than LMWH (more chances of bleeding than LMWH)
- Unfractionated heparin – extremely short acting
- Given S.C, OD, **fixed dose**
- Unchanged in urine – Since dose reduction required in renal failure
  - These drugs @ low doses → $X_a > II_a$ (prevents thrombus formation) @ high doses → $X_a = II_a$ (stop extension of thrombus)

UFH

i. Strongest organic acid in human body = R_X of overdose

↓

Protamine sulfate

↓

(Chemical antagonism)

strong base

↓

- UFH > LMWH
- No action on fondaparinux
- Anti II_a > Anti X_a

- Protamine sulfate – seldom required UFH – short acting

- Salient features
  - Extra-corporeal perfusion for heart surgery
  - High doses → anti-coagulant (overdoses avoided)
  - Anaphylaxis (with NPH insulin)

2. Highly negative charged at physiological pH

↓

Ionized agent

i. Not given P.O
  - Only via P.E
    - S.C – after 1hour
    - I.V – instant action
    - Interpersonal variation unstable PK features – BC2, metabolism combination of zero & first order
    - PK – Pharmacokinetic

↓

LMWH preferred

(Stable & predictable PK features)

Safe in renal failure (Anti-coagulants)

- Argatroban
- Warfarin
- Apixaban

A/E of heparin

1. Bleeding
   - More common in female, elderly, renal failure
   - apTT monitoring

     ↓
   - Target = 1.5 to 2.5 times the control

     ↓
   - Anti-X_a assay is preferred

     (Not confounded by acute phase reactants)
2. Osteoporosis
   - Osteoclastic activity > osteoblastic
   - Common in pregnant woman
3. Hyperkalaemia → zone glomerulosa suppression

Drugs causing hyperkalaemia

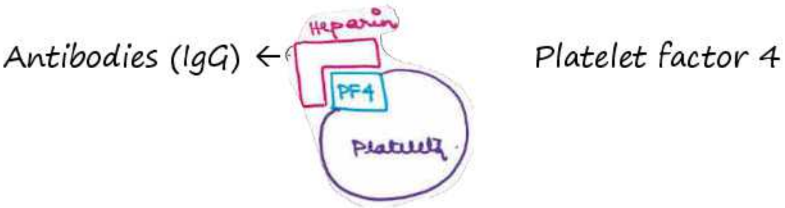
- Renin ⊖
- ACE ⊖
- ARB
- Digoxin
- K^+ sparing diuretics
- Heparin

4. Alopecia → Transient & reversible

   ↓

   "Telogen effluvium"
5. Hypersensitivity reactions
6. Thrombocytopenia → heparin behaves as

   (incomplete antigen)


Antibodies (IgG) ←
Heparin
PF4
Platelet
Platelet factor 4

- Decreased platelet count

  ↓

- Heparin induced thrombocytopenia

  ↓

- UFH > LMWH
- After 5-7 days of treatment
- Most common: Heparin from bovine lung
- Elderly, female, renal failure
- <1,00,000 / decrease in platelet count more than 50%
  - Treatment of HIT ↓ Severe ↓ Platelet infusion ↓ Avatrombopag (TPO-R ⊕)
  - Alternate anti-coagulant therapy ↓ Danaparoid, Argatroban, Fondaparinux

LMWH

Advantage

1. Stable PK
2. No need for aPTT monitoring
3. Less thrombocytopenia
4. Less osteoporosis
5. Long acting
6. Cancer associated thromboembolism

Disadvantage

1. No need for aPTT monitoring in renal failure
2. Effects not fully reversed by protamine
3. Less effective than UFH ↓
   - a. Catheter induced thrombosis
   - b. Cardiopulmonary bypass

Heparin resistance 00:52:52

- Therapeutic aPTT not achieved - >35,000 given per day
  - True resistance
    - Anti-factor X_a
    - aPTT
    - Sub-therapeutic levels
  - Pseudo resistance
    - Anti-factor X_a ↓ Therapeutic
    - aPTT ↓ Sub-therapeutic levels

Direct II_a inhibitors 00:55:01

Direct II_a inhibitors

Per oral

↓

Dabigatran

↓

Replacement of warfarin

Rapid onset of action

Direct specific competitive ⊖ of free & fibrin bound thrombin

- Least PPB
- DOC – Prophylaxis of stroke in A. sib
- Most common A/C – Dyspepsia

Overdose:

1. Idarucizumab (single dose) → Circulation
2. Dialysis

- Drugs interaction with amiodarone

Par enteral

↓

1. Lepirudin → Alternate therapy for HIT
   - Not used now
2. Bivalirudin – shortest acting ≈ 25min
   - ⊖ Platelet activation
3. Argatroban – safe in RF (liver excretion)

Direct X_a 01:00:15

1. Apixaban
2. Rivaroxaban
3. Betrixaban
4. Edoxaban

High plasma protein binding

↓

Interaction with P. glycoproteins +/-

- C/I in pregnancy
- Reduction in intracerebral haemorrhage (> warfarin)
- Both X_a & II_a ⊖ should not be stopped suddenly

Antidote

- Andexanet α
- Emergency
  - Prothrombin
  - Complex
  - Concentrate

Ciraparantag – Antidote for:

- UFH
- LMWH
- Dabigatran
- Oral X_a ⊖

Caplacizumab

- Used for acquired thrombotic thrombocytopenic purpura

Warfarin 01:04:48

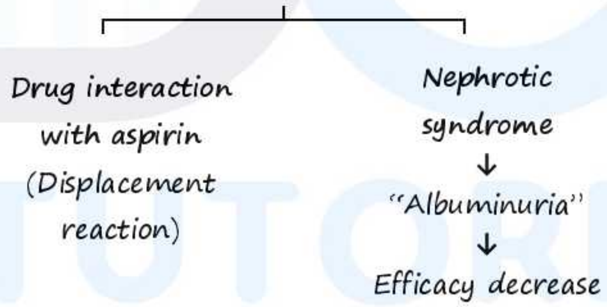
- Weak acid (Since, can be given P.O)
- ≈ 100% P.O bioavailability

- High PPB (Plasma Protein Bound) → Albumin (90-99%)
  - Acidic drug → albumin bound
  - Basic drug → α_1 acid glycoprotein

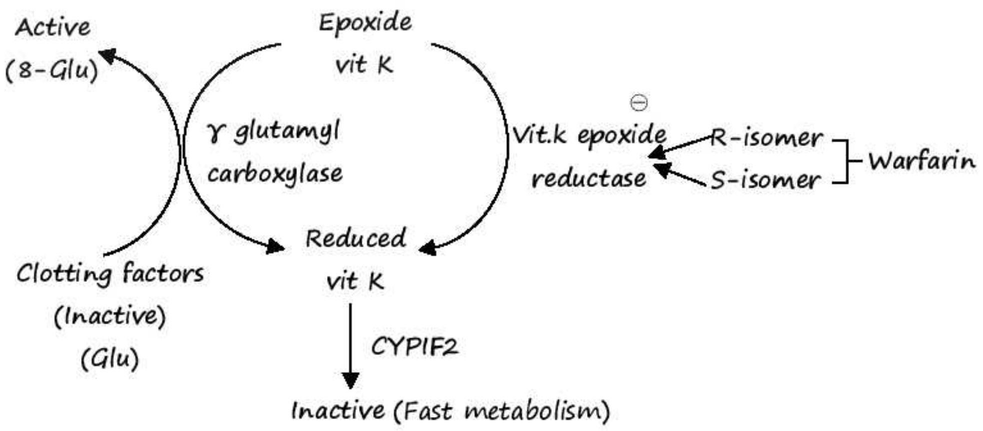
Drugs with ≈100% bio availability

- Isosorbide mononitride
- Warfarin
- Nizatidine
- Oxazolidinone
- Levofloxacin

- Albumin bound warfarin


Drug interaction with aspirin (Displacement reaction)
Nephrotic syndrome
"Albuminuria"
Efficacy decrease

DOC TUTORIALS
LOGIN FOR SUCCESS


Active (8-Glu)
Epoxide vit K
γ glutamyl carboxylase
Vit.k epoxide reductase
⊖
R-isomer
S-isomer
Warfarin
Clotting factors (Inactive) (Glu)
Reduced vit K
CYPIF2
Inactive (Fast metabolism)

- Inhibit vitamin K dependent clothing factors II, VII, IX, X

- S → 4 times more potent than R-isomer

  - R – $\xrightarrow[2C19]{2C9}$ Inactive

  - S – $\xrightarrow[2C19]{}$ Inactive

- Warfarin
  - ⊖ Clothing factors in order: VII → protein C → IX → Proteins → X → II

Protein C & S → Natural anti-coagulants

↓

Warfarin causes coagulation for first 3-4 days of therapy

(Transient hypercoagulable state)
(Protein C & S ⊖)

↓

Prevented by Heparin bridging

AllaTafreeh.com

A/E

- Bleeding (withdraw before 5 days of surgery)
- Skin necrosis
  - Breast, buttocks, thighs
  - In patients with protein C & S deficiency
  - Prevented by heparin bridging
- Purple toe syndrome – cholesterol emboli
- Teratogenicity

DOC TUTORIALS
LOGIN FOR SUCCESS

Teratogenicity

- I
  ↓
  Developmental ab Ⓝ
  ↓
  Warfarin embryopathy
  - Most common: Chondrodysplasia
  - Also: Nasal hypoplasia, hypertelorism
- II/III
  ↓
  CNS defects (MR)
  Mental Retardation

Drug Interaction (DI)
↓
Warfarin's action

- **Increased**
  - Cimetidine
    Amiodarone
    Sulfinpyrazone
    Macrolides
    ↓
    ⊖ **CYP**
  - Aspirin
    Salicylates
    Phenyl butazone
    ↓
    Displacement reaction
- **Decreased**
  - 1. Rifampicin
    2. Barbiturates
    ↓
    Microsomal enzyme inducers
  - OCP
    ↓
    ⊖ **AT**
    ⊕ **CF**

Interaction with anti-microbials (broad spectrum)
↓
Decreased intestinal flora
↓
Decreases vitamin K production
↓
Increase warfarin action

- Classically seen with regimen for H. pylori

Toxicity of warfarin

Toxicity
↓
Bleeding

Yes	No
↓ FFP Fresh Frozen Plasma	↓ Bleeding tendency ↓ INR

↓

≥ 20	9-20	5-9	<5
	↓ Vitamin K_1 2-3 mg P.O	Vitamin K_1 1mg P. O	Stop temporarily Restart @ low doses

For complete reversal: Vitamin K_1 5-10mg

DOC TUTORIALS
LOGIN FOR SUCCESS

Target INR

2.5	3.5
↓ For all other cases	↓ - Recurrent DVR/PE - Mechanical prosthetic mitral values

- Warfarin + paracetamol (>1.5g/ day)

  ↓

  Increase INR

  - Since alternative → CoX-2 ⊖ → Safe with warfarin

DOC TUTORIALS
LOGIN FOR SUCCESS

ANTI PLATELET

- ADP-R
- GP II_b/ II_a
- TxA_2
- PAR – I

- Clopidogrel & PPI (omeprazole) – drug interaction omeprazole inhibits 2C19 & decreases efficacy of clopidogrel
- ADP-R (P.E) – Cangrelor
- Abciximab – most potent
- Aspirin → ⊖ COX

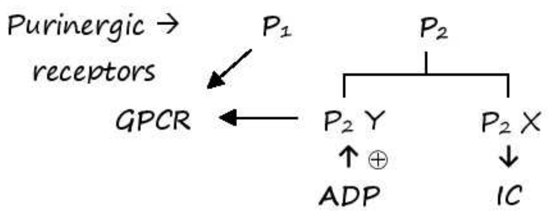
⊖ COX

⊖ TxA_2
↓
- Vasodilation
- ⊖ Platelet aggregation

⊖ PG I_2
↓
- Vaso constriction
- ⊕ Platelet aggregation

ADP-R ⊖ / P_2Y_{12}-R 00:05:10

- Non-competitive inhibitors



Non competitive

1. Irreversible → Thienopyridines

omeprazole ↓ ⊖

- Clopidogrel $\xrightarrow{2C19}$ Active
- Prasugrel $\xrightarrow{3A4}$ Active
- Ticlopidine

Pro drugs ↓ Converted to active form

a. Clopidogrel

- Bleeding
- T ½: 40 hours

b. Prasugrel

- Most potent P_2Y_{12} ⊖
- More bleeding
- C.I elderly/ stroke

c. Ticlopidine

- Most common A/E – "Diarrhoea"
- Also: Neutropenia/ Thrombocytopenia

2. Reversible → non-thienopyridines

a. Ticagrelor – P.O

DOC TUTORIALS LEARN FOR SUCCESS

b. Cangrelor → I.V

- Adjunct to PCI
- It is adenosine analogue

- Adenosine analogues
  - Adenosine
  - Cangrelor I.V
  - Cladribine

3. Etigrelor

GP II_b/ III_a $\ominus$ 00:13:00

i. Tirofiban/ lamifiban – non-peptide analogue

ii. Eptifibatide – Peptide analogue. Since, short acting

- Competitive $\ominus$ of GP II_b/ III_a

iii. Abciximab – monoclonal antibody

- All these have dose dependant anti-platelet activity

A/E

- Bleeding
- Thrombocytopenia
- Abciximab → non-selective integrin-R $\ominus$
  - $\ominus$ GP II_b/III_a – anti-platelet
  - $\ominus$ $\alpha_m\beta_2$ **anti-inflammatory**
  - $\ominus$ $\alpha_V\beta_3$ **anti-proliferatory**
- Abciximab

i. High affinity

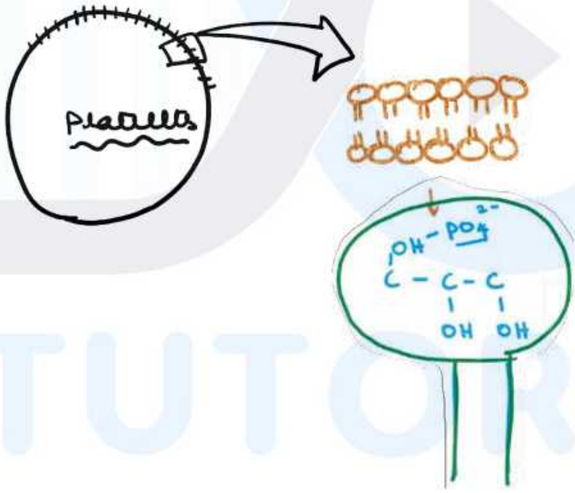
DOC TUTORIALS
LOGIN FOR SUCCESS

ii. Low dissociation

- Other drugs
  i. Low affinity
  ii. Rapid dissociation

Hereditary absence of GP_{2A}/ 3B Receptor
↓
Glanzmann
Thrombasthenia

Aspirin 00:19:06



DOI TUTORIALS
LOGIN FOR SUCCESS

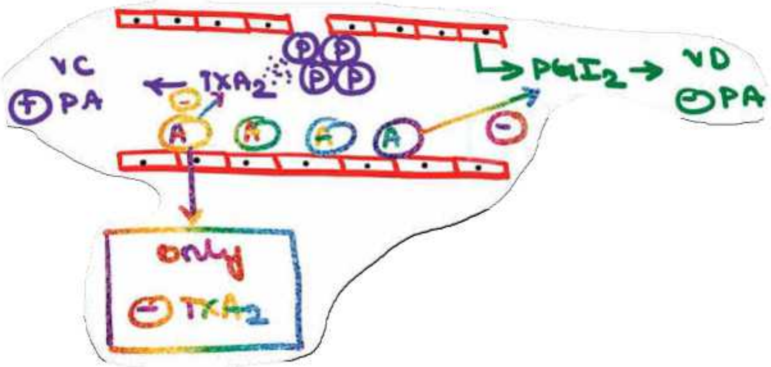
Phospholipase A_2

Arachidonic acid | Lysophosphatidase

Aspirin
Non-competitive (NC) →
(NC)
Irreversible (IR) →
Inhibitor

PG G_2
↓ CoX
PGH_2
⊖↓ CoX
T_XA_2
↓ T_XA_2 synthetase

1. Vaso constriction
2. Platelet aggregation



- T_XA_2 → Platelets synthesize (CoX)
-
- PG I_2 → Endothelial cells (CoX)

Aspirin non-comp & irreversible

  - Has nucleus → resynthesize CoX
- Platelets → No nucleus → Blockade is irreversible

Aspirin

- At low dose → anti-platelet
  - As T_XA_2 ⊖ >> PG I_2 ⊖
  - At low → CoX1 ⊖
- At medium & high dose
  - Anti-inflammatory
  - Niacin toxicity
  - ACE ⊖ induced dry cough

→ CoX-1 & CoX-2 ⊖

PAR-1 ⊖ Protease activated receptor (Thrombin-R)

00:29:48

- Vorapaxar
- Atopaxar

Dipyridamole

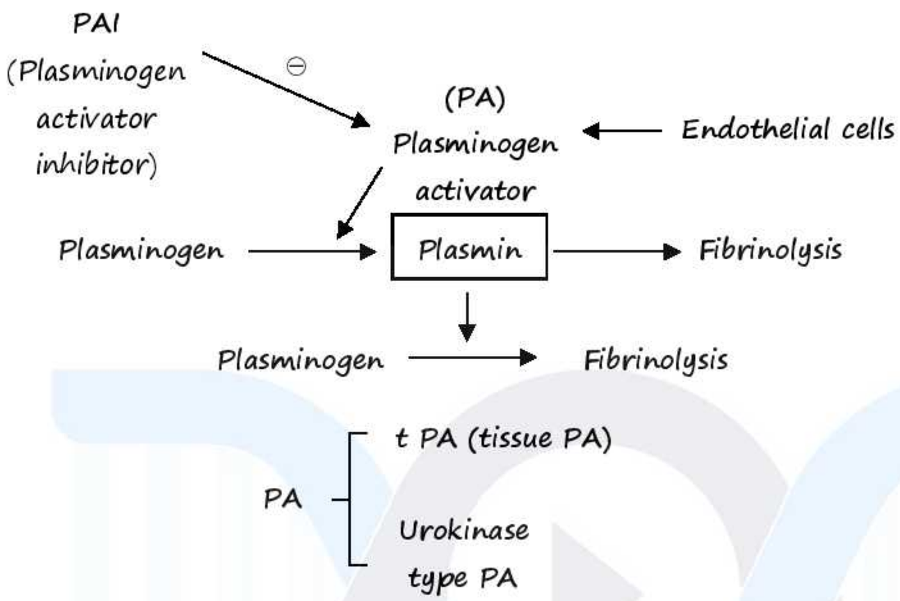
- ⊖ adenosine reuptake by RBC
- ⊖ PDE 3

Dextran 40/75

- Anti-platelet activity

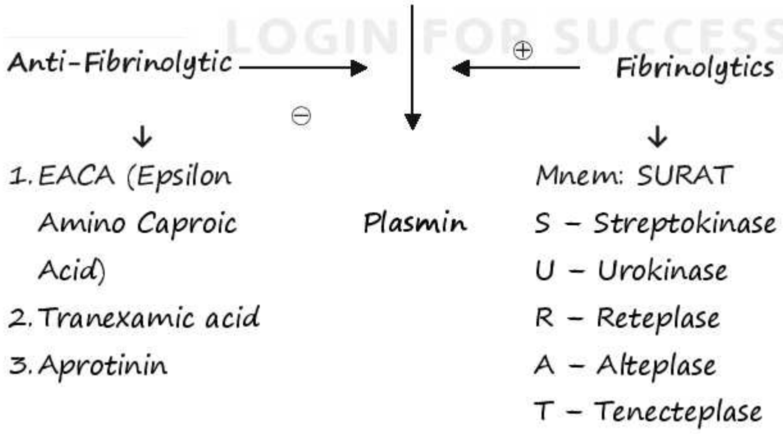
FIBRINOLYTICS, HEMATINICS

Fibrinolytics 00:00:26


PAI
(Plasminogen activator inhibitor)
⊖
(PA) Plasminogen activator
Endothelial cells
Plasminogen
Plasmin
Fibrinolysis
Plasminogen
Fibrinolysis
PA
t PA (tissue PA)
Urokinase type PA

Fibrinolysis inhibitors

- PAI (Plasminogen activator inhibitor)
- α_2 – anti plasmin
- TAFI (Thrombin Activatable Fibrinolysis Inhibitors)


Anti-Fibrinolytic
⊖
⊕
Fibrinolytics
Plasmin

Anti-Fibrinolytic
1. EACA (Epsilon Amino Caproic Acid)
2. Tranexamic acid
3. Aprotinin

Fibrinolytics
Mnem: SURAT
S – Streptokinase
U – Urokinase
R – Reteplase
A – Alteplase
T – Tenecteplase

Fibrinolytics
- Stroke – Within 4-5 hours
- MI – Within 12 hours
  ↓
  Acute coronary intervention (Preferred)

- Tenecteplase is more commonly used

1.Streptokinase

- Derived from β-hemolytic group c streptococci
- Non-enzymatic degradation of fibrin

Demerits

- Non-selective
  - Fibrin bound plasminogen
  - Circulating plasminogen
- Short acting
- Hypersensitivity reactions (on repeated administration)

2.Urokinase

- Derived from human urine
- Non-enzymatic degradation like streptokinase
- Costlier

3.Alteplase (t-PA analogues)

- Enzymatic degradation

- Short acting → I.V infusion (90 min)

  (30-180 min)

  (Pulmonary embolus → I.V bolus)

- Plasminogen Activator Inhibitor (PAI)

  - 1
  - 2 ⊖ → short acting

4.Reteplase & Tenecteplase

Long acting

- Reteplase
  - ↓
  - Repeated after 15-30 min
- Tenecteplase
  - ↓
  - I.V bolus (Single)

- Resistant to PAI
- Specific to "Fibrin bound plasminogen"

- Streptokinase
- Urokinase
- Alteplase

Short acting ↓ I.V infusion

- Reteplase
- Tenecteplase

Long acting ↓ I.V bolus

A/E

1. Bleeding
2. Following fibrinolysis

↓

- IM injection CI
- Intra-arterial injury – C.I
- I.V injection → Needs atleast 10min of local compression

3. Hypotension/ allergic reaction

Contraindications of fibrinolysis

Conditions predispose to intra cranial bleeding

↓

Example:

- Haemorrhagic stroke
- Intracranial neoplasm
- Recent neuro surgery
- Brain trauma (<10 days)
- Uncontrolled HTN (>185/100)

Conditions predispose to massive haemorrhage

↓

Example:

- Major surgery (<10days)
- Current major bleeding

Haematinics 00:19:55

RBC

- Erythropoietin ⊕
  - Drugs
    - Darbopoietin α
    - Epoietin α

WBC

i. G-CSF
- Drug:
  - Filgrastim (Reg)

ii. GM-CSF
- Drug:
  - Sargramostim

Platelets

i. IL-II
- Drugs
  - Oprelvekin

ii. Thrombopoietin
- Drugs
  - Altrombopag
  - Avatrombopag
  - Romiplostim

Treatment of haemophilia 00:23:00

- Newer drugs

Fitusiran

- Induce thrombin generation
  - RNA interference
  - ⊖ AT synthesis
  - Treatment: Hemophilia A/B

Emicizumab

- Monoclonal antibody
- Mimic factor XIII

Concizumab

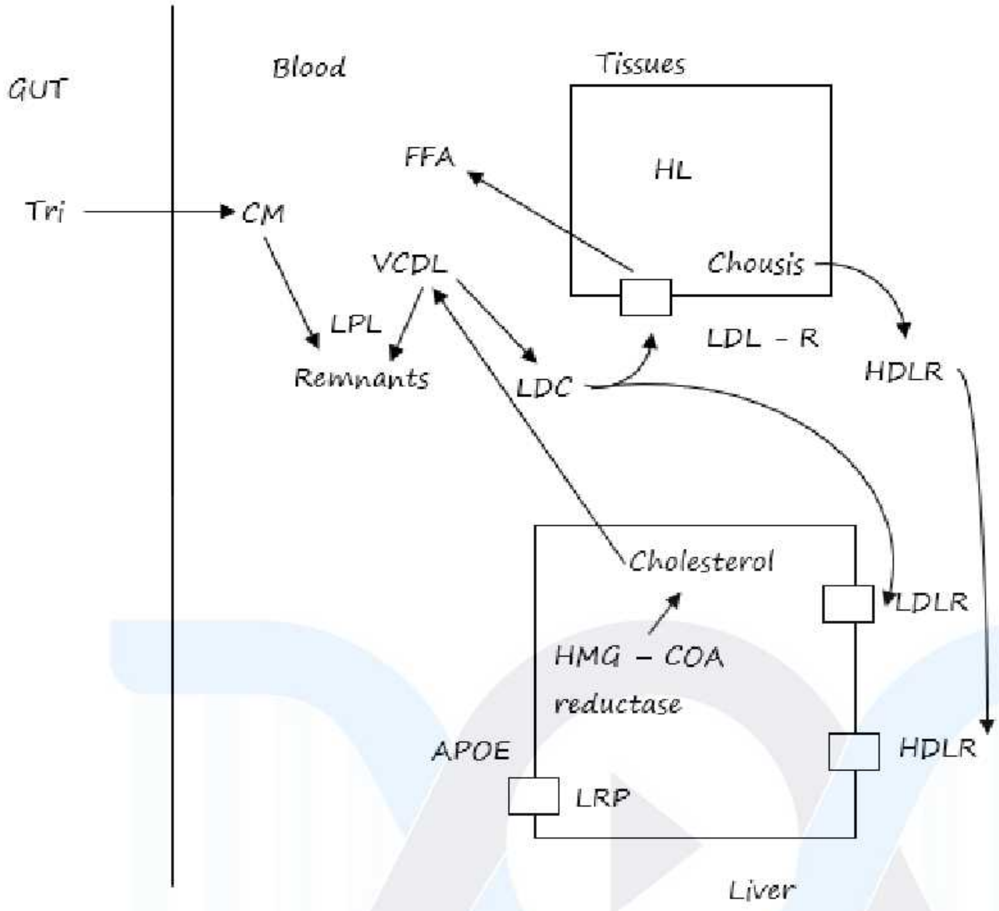
- Anti-tissue factor pathway inhibitor (TFPI) mab

Fostamatinib

- Tyrosine kinase ⊖
- Treatment:
  - Chronic immune thrombocytopenia

DRUGS USED FOR DYSLIPIDEMIA – I

- The triglycerides present in the gut are **bind with chylomicrons in blood.**
- Remnants are present in blood, LIPOPROTEIN LIPASE acts on Chylomicrons and forms remnants
- The remnants act on receptors on surface of liver, **LDL Receptor protein (LRP) aided with molecule of apo-E**
- HMG-COA reductase enzyme is present in liver, involved in synthesis of cholesterol in liver.
- This cholesterol synthesized is in the form of VLDL
- **Cholesterol synthesized in tissues in the form of HDL form**
- VLDL can be converted to LDL, this LDL acts on receptors (LDL-R) on tissues & liver.
- **HDL will act on receptors HDL - R**
- LDL absorbed from the tissue gets converted into free fatty acids (FFA) with the help of enzyme – Hepatic Lipase.


GUT
Blood
Tissues
Tri
CM
FFA
HL
VCDL
Chousis
LPL
Remnants
LDC
LDL - R
HDLR
Cholesterol
LDLR
HMG - COA
reductase
APOE
LRP
HDLR
Liver

i. **Familial combined hyperlipidemia**, increased VLDL (apo-B), it tends to increase LDL

ii. **Familial hypertriglyceridemia** due to **LPL inhibition**. Increased triglyceride rich VLDL will be present

iii. Remnant Removal Diseases (familial days' beta – lipoprotein

- Due to a PDE deficiency
- Increased IDL

Familial Hypercholesterolemia 00:04:57

- Increased total cholesterol
- Increased LDL
  1. Familial combined hyperlipidemia – treatment – statins – (± Fibrates)
  2. Familial Hypertriglyceridemia – treatment – fibrates (rare → Niacin)
  3. Remnant removal disease– treatment – Statins (± fibrates)
  4. Familial hypercholesterolemia – treatment – statins (± ezetimibe), **(± PCSK- 9 inhibition)**
  5. **Homozygous familial hypercholesterolemia** – treatment – LDL – apheresis)

Statins 00:09:28

- HMG –COA reductase inhibitor, this inhibition is dose dependent
- HMG – COA reductase inhibition

Competitive reversible inhibition cholesterol

(except for lovastatin)

- lovastatin – noncompetitive & irreversible
- all these drugs have pleiotropic effects
- Has got inflammatory atheroma progression

decreased synthesis of liver

↓

- increases LDL – R synthesis (increased drugs night time)

↓

- Decreases blood LDL
- decreases total cholesterol [within 1 month of treatment]

- Lovastatin
- Simvastatin

PRODRUGS

- **Fluvastatin – maximum per oral bioavailability**
- Pravastatin – decreases fibrinogen, less drug food interaction
- Atorvastatin
- Rosuvastatin

Long t1/2 (Rosu) Ator)

- Pitavastatin
- Rosuvastatin

Potency (pitava > Rosura)

Adverse drug reaction 00:16:45

- Increased AST/ ALT
- Increased creatinine phosphokinase
- Myositis (rare) –more with fibrates / raisin / protease inhibitors / Antibiotics)
- Modest increases chances of new onset diabetes mellitus

Fibrates 00:19:09

- Fenofibrate

PPAR – alpha activator

↓

Increased expression of LPL / Apo A1

Decreased expression of Apo C11

↓

Increased LDL – R

↓

- Decreased blood LDL
- Increased HDL

  Structure of fibrates – resembles short chain fatty acids
- It tends to decreases blood fibrinogen & decreases cute concentration
- Decreased blood fibrinogen enhances oral anticoagulant
- Decrease in rate cute concentration – gemfibrozil used in ceramic nephrotic pts
- Other fibrates are contraindicated in severe hepatic / renal failure (as it is excreted unchanged) more risk of myositis

- Q. When to add fibrates with statins?

  i. Persistent hypertriglyceridemia

  ii. Low HDL.

DRUGS USED FOR DYSLIPIDEMIA -II

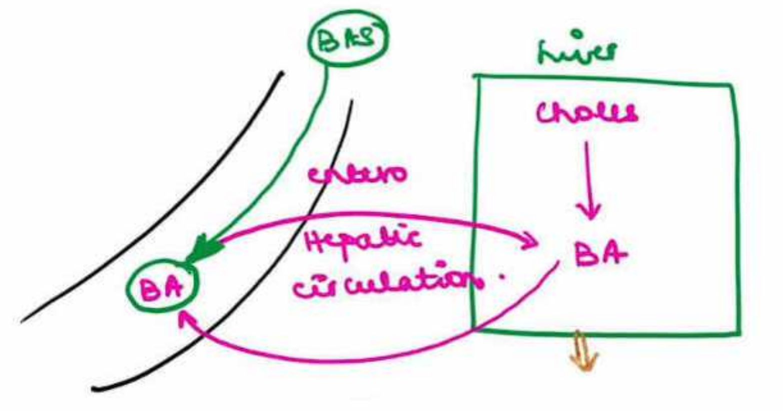
- Cholesterol has the capacity to synthesis the bile acids and these bile acids are going to be excreted out in the intestine, it moves from small intestine to large intestine then gets absorbed into blood again and moves into the liver. This is enterohepatic circulation. Bile acid levels are maintained by the help of this enterohepatic circulation.
- Enterohepatic circulation increases the half-life of bile.

Bile acid sequestrants: 00:00:11

- We give these drugs via **per oral route**
- BAS gains entry into intestine, binds to bile acid and prevents enterohepatic circulation so bile acid is secreted out of the body and the liver needs to synthesis the bile acid again leading to the cholesterol pool in the body to be lost.
- More cholesterol gets converted to bile acids, leading to decreased intracellular cholesterol in hepatocytes
- Leads to increased LDL-Receptor upregulation **causing decreased LDL but Increased TGs.**
- If the de novo cholesterol levels are going to be reduced in the liver the liver will thrive on the LDL which is present in the blood it takes up all the LDL and utilizes it for the production of bile acid, but

unfortunately Triglyceride levels tend to increase because of these Bile acid sequestrants, as they lead to hypertriglyceridemia, **they are not the 1st drugs of choice in treatment of hypercholesterolemia.**

- In the liver cholesterol is converted to bile acid.
- The bile acid gets entry into the intestine.
- From the intestine the bile acid is reabsorbed into blood and goes to the liver – enterohepatic circulation.
- **The bile acid sequestrants come and bind to the bile acids in the intestine and prevent reabsorption.**
- This causes more cholesterol to get converted into bile acid in liver.
- enterohepatic circulation is prevented by Bile acid sequestrants.
- More cholesterol is converted to bile acid leading to decrease in intracellular cholesterol in hepatocytes.
- Decrease in the intercellular cholesterol in the hepatocytes leads to increase in LDL receptor up-regulation leading to decrease in LDL but increase in Triglycerides. (Hence these drugs are not preferred in Triglyceridemic PATIENTS)
- All these Bile acid sequestrants are anion exchange resins.


BAS
liver
Choles
BA
entero
Hepatic
circulation.
BA

BA re excreted

(enterohepatic is called $\ominus$

by BAS)

↓

More cholesterol BA

The drugs are:

- **Colesevelam** – it is not an anion binding resin
- **Colestipol** – anion binding resin, given as capsule form
- **Cholestyramine** – anion binding resin, given as powder form.

Bile acid sequestrants:

- Drug interactions
  1. Warfarin
  2. digoxin
  3. Thiazide
  4. Phenobarbitone
  5. T3/T4

- BAS tend to bind with the above-mentioned drugs and **prevent reabsorption of these drugs**.
- Prevention: these drugs should be taken 1hr before or 4hrs after cholestyramine.
- **These drugs bind with fat soluble vitamins in the gut (vit A, D, E, K)**
- Vit K is affected most and there is **vit K responsive prolongation of prothrombin time**.
- Adverse effect: as bile acids are not getting reabsorbed there is more amount of bile acid accumulated in the intestine which will be excreted out so patient will have constipation.

Ezetimibe: 00:07:49

- It prevents the absorption of dietary cholesterol.
- It is a prodrug.
- It gets converted to **Ezetimibe glucuronide (longer t1/2)**
- Mechanism of action: it **binds with Niemann Pick C1 like-1 protein (NPC1L1)**. it is a transporter responsible for absorption of cholesterol (dietary fat) and it is inhibited by ezetimibe.
- Rather than increasing the dose of statins we prefer to give ezetimibe along with statins as it has very less adverse, effects similar to placebo.

- The efficacy increases with statins, better than high dose of statins.

Niacin: 00:10:22

- It is an anti-lipolytic agent in the adipose tissue.
- It decreases free fatty acid levels in the blood which decrease the LDL, VLDL, and apo A molecule.
- Adverse effects: **G.I related affects, skin flushing.**
- Treatment: Aspirin (blocks PG), **Laropiprant** (PGD2 antagonistic agent)
- **Usually, Niacin is not recommended due to decreased efficacy and other adverse reactions.**

Other adverse effects:

- Development of severe hepatotoxicity
- Gout- hyperuricemia
- Insulin sensitivity is decreased.
- Acanthosis nigricans
- Maculopathy

Newer Drugs 00:13:49

ACIPIMOX

- It is a long-acting agent
- **It does not decrease apo A**
- Better tolerated
- Less efficacy so not prescribed.

OMEGA 3 FATTY ACIDS

- Mostly seen in oily fishes
- It decreases the TG levels (CAD prevention)
- It increases LDL levels

ORLISTAT

- **It decreases blood cholesterol levels and blood glucose levels**
- Fat absorption is going to be inhibited so fat-soluble vitamins absorption will also be inhibited **so supplementation of these vitamins is necessary along with orlistat.**

ALPHA-TOCOPHEROL ACETATE (VITAMIN E)

- Acts as an anti-oxidant and prevents LDL oxidation leading to decrease in atheroma formation

Icosapent

- It is used as an adjunct to diet in severe Hypertriglyceridemia, it decreases VLDL-TG
- It is given as Per Oral route, tablet form.
- 4g/day is the usual dose.

LOMITAPIDE

- It inhibits microsomal triglyceride transfer protein (MTP) that is responsible for the assembly and secretion of VLDL this leads to the blockage in VLDL assembly and secretion in Liver.

- Causes decrease in VLDL and Chylomicron levels in body.

LDL-R

- LDL receptors are **degraded by PCSK-9 enzyme (pro protein convertase Subtilisin kexin-9)**
- **ALIROCUMAB** and **EVOLOCUMAB** are monoclonal antibodies that are PCSK-9 inhibitors.
- Given to patients on statins with uncontrolled cholesterol.
- Both these drugs are given by sub cutaneous route on every 2-4th weekly basis. Administered every 4th night subcutaneously.
- Evolocumab can be administered as monthly injection of 420mg. (Recently approved)
- It increases the expression of LDL receptors and thereby decrease LDL levels in blood.

BEMPEDOIC ACID

- It inhibits the synthesis of LDL cholesterol.
- **MOA: it inhibits ATP citrate lyase enzyme**
- Adverse effects:
- It may cause upper respiratory tract infections.
- It may cause hyperuricemia.

MIPOMERSEN

- It is an antisense oligo nucleotide, it inhibits the synthesis of apo B100 translation process, it is an orphan drug

VOLANESORSEN

- It is an antisense oligo nucleotide, it inhibits the synthesis of c3 translation process, it is an orphan drug.

CETP (CHOLESTEROL ESTER TRANSFER PROTEIN) INHIBITORS:

- Torcetrapib
- Dalcetrapib
- Evacetrapib
- Anacetrapib
- Obicetrapib
- They prevent the conversion of HDL to LDL so it leads to HDL accumulation and HDL increase and decrease in TG and decrease in LDL levels.

DRUGS AFFECTING HYPOTHALAMUS

Drugs affecting hypothalamus 00:00:59

- Hormone: a substance produced in a part and carried by blood to different parts where it produces its effect.

GHRH and somatostatin 00:01:11

Control of growth hormone (GH)

Growth Hormone Releasing Hormone (GHRH)

↓

a. Rapidly increases GH levels

b. Some GHRH analogues are

i. Sermorelin

↓

Currently withdrawn

ii. Examorelin

↓

Used to treat HIV wasting and lipodystrophy

Somatostatin

↓

a. Decreases GH levels

b. It is called "universal hormone inhibitor"

c. The hormones it inhibits are: - mnemonic: GIVE IT

- GH
- Insulin
- Gastrin
- VIP
- Glucagon
- TSH

Somatostatin analogues 00:01:11

Somatostatin analogues

- Octreotide
  - ↓ Given sc/im./iv
  - ↓ Uses are
    - Acromegaly
    - Gastrinoma
    - Glucagonoma
    - Islet cell tumor
    - VIP. Oma
    - Oesophageal varices
    - Thyrotrope adenoma
- Lanreotide
  - ↓ given deep S.C as auto gel Formation
  - ↓ Uses are
    - Neuroendocrine tumors
    - Carcinoid syndrome
- Pasireotide
  - ↓ given S.C
  - ↓ Used for Acromegaly

- Adverse effects of somatostatin analogues
  - a. Most commonly G.I related disorders
  - b. Gall stones
  - c. Bradycardia
  - d. Q - T prolongation
  - e. Hyperglycemia (maximum in Pasireotide, minimum in Octreotide & Lanreotide)

Drugs controlling gonadotropins 00:07:08

- Gonadotropin releasing Hormone (GnRH) analogues

a. 2 types of therapy

2 types of therapy

Pulsatile therapy
↓
Increases LH and FSH
↓
Used to treat infertility

Long term continuous therapy
↓
decreases LH and FSH
↓
causes hypogonadism

b. Some GNRH analogues are: -

- Gonadorelin
  - HCl type used for hypogonadism
  - Acetate type used for infertility
  - Used to diagnose pituitary or Hypogonadotropic Hypogonadism
- Naferelin
- Buserelin

} Can be given by nasal spray

- Gosrelin → given S.C/I. V/ implant
- Leuprolide → long acting
- Used for treatment of Ca prostate, Ca Breast, endometriosis, fibroid uterus

- **Naferelin, buserelin and Goserelin are the drugs of choice to suppress gonadotropin secretions in precocious puberty.**

GnRH antagonists 00:08:01

i. Cetrorelix
ii. Ganirelix
iii. Degarelix

] preferred over GnRH analogues for induction of hypogonadism as recovery is faster

- Cetrorelix and Ganirelix have been approved for controlled ovarian hyper stimulation
- Degarelix used to treat advanced Ca. prostate

Drugs controlling Prolactin secretion 00:12:54

i. Prolactin is increased by

↓

Prolactin Releasing Factor (PRF)

↓

PRF is increased by

ii. Prolactin is inhibited by

Prolactin inhibitory Factor (PIF)

↓

PIF is increased by

- D_2 agonists
- Bromocriptine
- Cabergolide
- Pergolide
- Quinagolide

] ERGOT DERIVATIVES

- Adverse effects of Ergot derivatives
  - Vasospasm
  - Cardio pulmonary fibrosis
- Quinagolide is relatively safer

Cabergolide

- Most D_2 selective agent
- Long acting
- Adverse effect → postural hypotension

DRUGS AFFECTING ANTERIOR PITUITARY

Growth hormone 00:00:24

- Growth hormone is secreted by anterior pituitary.
- Growth hormone has certain GH analogues and certain GH antagonistic agents.

Somatropin 00:00:40

- Somatropin is a drug which is a GH analogue agent.
- Somatropin mimics the actions of GH

Adverse effects

- These drugs increase the intra cranial tension
- They may cause scoliosis
- There might be development of carpal tunnel syndrome
- There may be slipped epiphysis.

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Peg-visomant 00:01:22

- Peg-Visomant given via Subcutaneous route
- GH acts by the help of 2 different receptors.
- The two different GH receptors must fuse together and only if they fuse together there will be production of proteins.
- Peg-Visomant binds with a single part of the receptor and it blocks that receptor leading to no fusion between the two GH receptors. Thus, antagonizing the action of GH.
- Fusion of the 2 GH receptors is called as homo dimerization.

- Peg-Visomant prevents homodimer formation.

Uses

- These drugs are used in acromegaly due to pituitary edema.

Adverse effects

- Peg-Visomant causes visual disturbances.
- Recombinant IGF-1(insulin like growth factor) - mecasermin

Gonadotropins 00:03:14

Gonadotropins

- We have 2 different groups:
  - i. Menotropins
  - ii. HCG (human chorionic gonadotropin)

Menotropins

- It is LH+FSH mixture
- It is derived from post-menopausal urine
- It is used for ovulation induction

TUTORIALS LOGIC FOR SUCCESS

HCG

- It is derived from pregnant woman urine
- It stimulates gonadal steroidogenesis

Adverse effects

- Both Menotropins and HCG cause ovarian hyper stimulation and ovarian enlargement

Drugs affecting gonadotropins 00:04:41

i. FSH derived from pregnant urine- Urofollitropin

ii. Recombinant FSH- Follitropin ∝/β

iii. Recombinant LH - luetropin ∝

iv. Recombinant HCG- Choriogonadotropin ∝

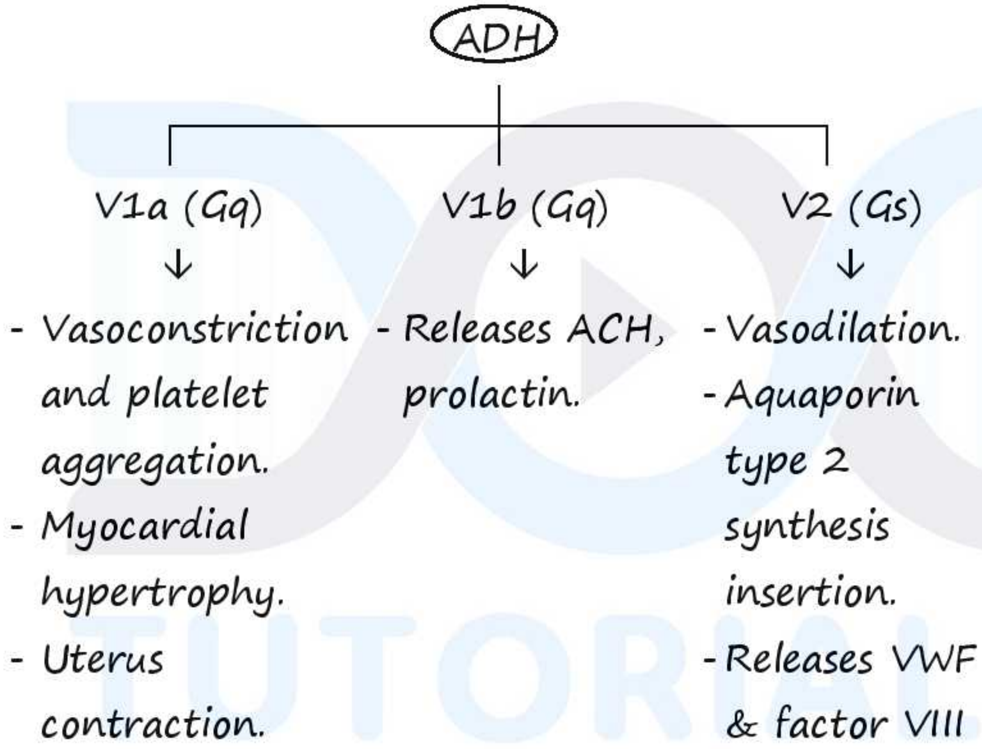
v. Bovine + human ACTH – cosyntropin

- Cosyntropin is the drug of choice for infantile spasm not associated with tuberous sclerosis.

DRUGS AFFECTING POSTERIOR PITUITARY

Anti-Diuretic Hormone 00:00:16

- Two types of receptors V_1 & V_2.
- V1 is further divided into V_{1a} & V_{1b}



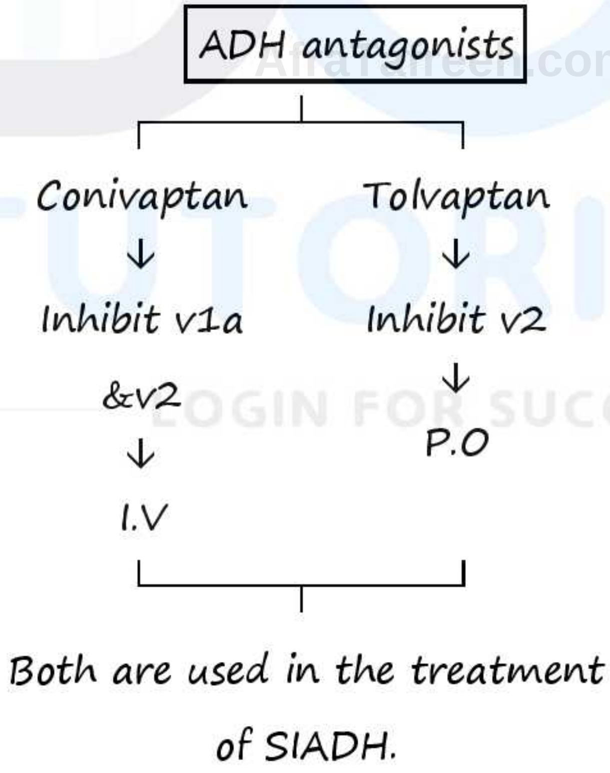
V1a (Gq)
- Vasoconstriction and platelet aggregation.
- Myocardial hypertrophy.
- Uterus contraction.

V1b (Gq)
- Releases ACH, prolactin.

V2 (Gs)
- Vasodilation.
- Aquaporin type 2 synthesis insertion.
- Releases VWF & factor VIII

ADH analogies

Layperson	Terlipressin	Desmopressin
- V1 = V2	V1 > V2	V2>>V1
- Parenteral route	Parenteral route (recommended for acute variceal bleeding& hepato- renal syndrome).	Nasal route/parenteral route used for craniogenic DI nocturnal enuresis mild hemophilia A.


ADH antagonists
Conivaptan
↓
Inhibit v1a &v2
↓
I.V
Tolvaptan
↓
Inhibit v2
↓
P.O
Both are used in the treatment of SIADH.

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- Drugs that after ADH secretion:

  i. Clofibrate → increases ADH secretion.

ii. Lithium/Demeclocycline → decreases ADH secretion.

iii. TCA/chlorpropamide → Increases ADH receptor sensitivity.

Oxytocin 00:06:42

- Responsible for labor → causes contraction of fundus of uterus while relaxing the lower segment of uterus.
- Milk ejection.
- No activity on lacto genesis.
- Responsible for induction & augmentation of labor.
- Useful to induce abortion in 2nd trimestral.
- Oxytocin challenge test – for fetal heart rate.
- Contra indicated in:
  i. Contracted pelvis.
  ii. Obstructed labor.
  iii. Malpresentations.
  iv. Cardiac diseases /renal diseases (as oxytocin acts on V_2 reception and cause side effect like fluid retention).
  v. Hypodermic states.
- Oxytocin receptor antagonist:
  i. ATOSIBAN → relaxed uterus.
  ii. Preterm labor.

DRUGS USED FOR HYPOTHYROIDISM

What are the Subtype of receptor T_3, T_4?

- Intra Cellular Receptor
  - But for TSH, TRH is going to be released from hypothalamus TRH stimulates anterior pituitary, from there TSH is going to be released out. This TSH accumulates on certain receptors on the surface of the thyroid gland
  - Thyroid in turn releases out T_3 and T_4 which is further going to cause different actions

- Hypothalamus
  ↓
  TRH
  ↓ Gq coupled receptor
  Anterior Pituitary
  ↓
  Releases TSH
  ↓ Gs coupled receptor
  TSH on follicular cells of thyroid gland
  ↓
  Iodide transport into the thyroid gland
  ↓
  Iodination of tyrosine residues (which is already been accumulated in tyrosine follicles)

- This leads to formation of

1. Monoiodo Tyrosine ⎤ Forms T_3 Molecules
2. Di iodo tyrosine ⎦⎤ Forms T_4 Molecules
3. Di iodo tyrosine ⎦

- MIT (Monoiodo tyrosine) + Di iodo tyrosine (DIT) = T_3 formation
- DIT +DIT =T_4 formation
- This reaction is enzyme by peroxidase enzyme, this reaction is organification and coupling reaction
- T_3 and T_4 release out in the periphery (blood)
- In blood the most important thyroxine is T_3
- In blood T_4 is further converted to T_3
- T_4 gets converted to T_3 this is called as de iodination reaction and the enzyme is deiodinase
- These react on nuclear receptors because of their reaction these is increased. Increased ATP hydrolysis, Increased Basal Metabolic rate, Increased oxygen consumption
- This thyroxine is broken down by glucuronidation & sulphation

- Deiodinase enzyme is converted into

1. D_1
2. D_2
3. D_3

  - Deiodinase$_1$ & Deiodinase$_3$ are responsible for the conversion of T_4 to T_3

  - D_3 is responsible for the conversion of T_4 to reverse T_3
- This DE iodination is inhibited by
  - Propranolol
  - Glucocorticoids
  - PTU (propyl thio uracil) orient
  - Cd towards D_1
  - Amiodarone (D_1 & D_2)

Difference Between T_3 T_4 00:06:45

T_3	T_4
T_3 is the most important ligand	Weak binding to receptors
5-10% bound with Thyroxine binding globulin (TBG)	90-99% is bounded with TBG +pre-albumin Synthetic T_4 is levothyroxine
T1/2 → 1 day	t1/2 → 5-7 days
Synthetic T_3 available liothyronine	Passive protein binding increases the duration of action, t1/2 is also going to be increased

- Anything which was bounded with the protein cannot be excreted out easily. Titration does not depend on PH it depends on size of the molecule so T_4 is bounded by the protein, so t1/2 is increase, duration of action increases

Synthetic T_3

- Liothyronine has good absorption (iv).

Synthetic T_4

- Levothyroxine has long t1/2, favorable T_4: T_3 ratio, Given OD (single tablet per therapy). This drug is given by fasting route as absorption is higher

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Adverse Effect 00:10:21

---

1. Iatrogenic hyperthyroidism
2. Nervousness, anxiety (due to hyperactivity of thyroid)
3. Angina, Myocardial infarction, arrhythmia (Atrial fibrillation especially when given with pilocarpine)

Never Drug Preparation 00:11:10

---

i. Liotrix → Contains T_4 & T_3 = T_4: T_3 ratio is 4:1

ii. Thyroid USP → Contains T_4, T_3, MIT & DIT.

- MANAGEMENT OF MYXEDEMA COMA & THYROID STORM

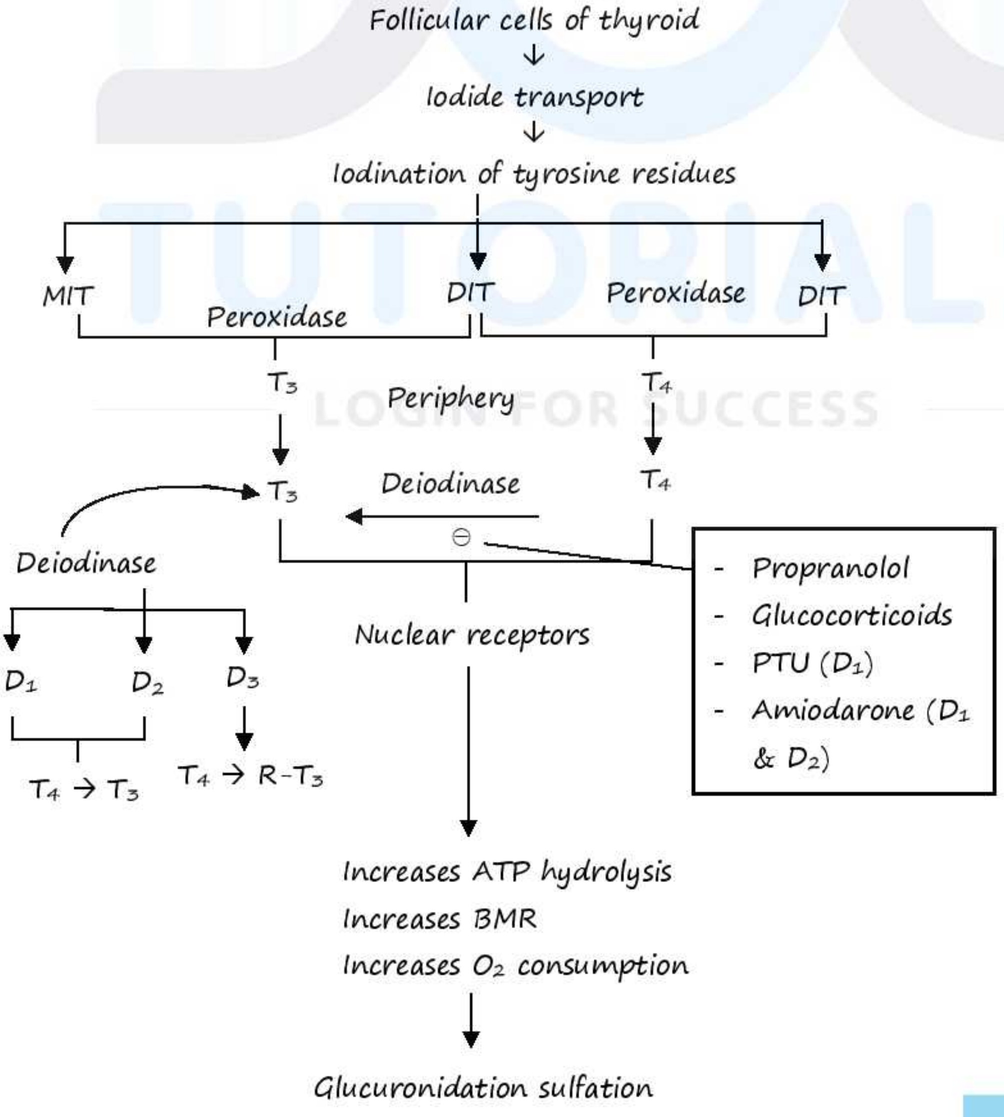
- Drug of choice is l-thyroxine (T_4) 200-500 μg i.v. followed by 100 μg i.v. OD till oral therapy can be instituted. Some authorities recommend adding low dose i.v. T_3 10 μg 8 hourlies in younger patients with no arrhythmia or ischemia. Alternatively, oral T_4 500 μg loading dose followed by 100–300 μg daily may be used, but in severe hypothyroidism, oral absorption is delayed and inconsistent.
- Other essential measures needed are—warming the patient, I.V. corticosteroids to cover attendant adrenal insufficiency, ventilatory and cardio vascular support, correction of hyponatremia and hypoglycemia.

DRUGS USED FOR HYPERTHYROIDISM

4 Major Groups of Antithyroid Drugs

- Drug Decreasing synthesis of thyroxine → **Thioamides** (PTU, Methimazole & Carbimazole)
- Drug inhibiting iodide trapping → **Anions** (Thiocyanate Fluoroborate, Perchlorate)
- Drug causing thyroid constipation → Prevents hormone release → Iodine (fastest acting)
- Drug destroying thyroid tissue → Radioactive iodide

Thioamides 00:02:01


Follicular cells of thyroid
Iodide transport
Iodination of tyrosine residues
MIT
Peroxidase
DIT
Peroxidase
DIT
T_3
Periphery
T_4
T_3
Deiodinase
T_4
⊖
Deiodinase
D_1
D_2
D_3
$T_4 \rightarrow T_3$
$T_4 \rightarrow R\text{-}T_3$
Nuclear receptors
- Propranolol
- Glucocorticoids
- PTU (D_1)
- Amiodarone (D_1 & D_2)
Increases ATP hydrolysis
Increases BMR
Increases O_2 consumption
Glucuronidation sulfation

- MOA → Blocks peroxidase enzyme blocks organification & Coupling
- Propylthiouracil belong to thioamides but it has an additional MOA → It blocks Deiodinase enzyme,

- Drugs: – PTU, Methimazole, Carbimazole (Prodrug, converted to its active which is methimazole)

Propylthiouracil	Methimazole
Less potent	Most potent & hence DOC for Graves' disease
Advantages - Blocks deiodinase enzyme - Safe in pregnancy	Teratogenic → Choanal & esophageal atresia, fetal goiter, Aplasia cutis etc.
Both PTU & Methimazole cause	Rash, Thrombocytopenia, Agranulocytosis

- Hepatocellular damage is more with PTU than methimazole

Anions

- MOA – Prevent iodide trapping
- Drugs:
  i. Thiocyanate
  ii. Fluoroborate
  iii. Perchlorate

  All are single negatively charged anions

- These single negatively charged anions compete with I (Iodine) for transport into the thyroid follicle

Iodide

- MOA → Block hormone release --. hence hormone fastest acting drugs trapped in the follicles

Iodide might cause

- Hypothyroidism
  ↓
  Wolf – Chaikoff effect (Drug induced hypothyroid)
- Hyperthyroidism
  ↓
  Jod – Basedow effect (Drug induced hyperthyroid

Uses of iodine

- Used pre-operatively to render the gland less firm & less vascular

Radioactive Iodine 00:08:56

- MOA destroy thyroid tissue
- I^{131} → Releases β & γ rays inside the gland →Destroys thyroid tissue
- I^{131} uses: Both diagnostic & therapeutic purposes
- I^{123} uses; Only for diagnostic purpose as it only releases γ (Gamma) rays
- Duration of action → 8days
- I^{131} is used in surgical ablation of thyroid

Adverse Effects

i. Hypothyroidism

ii. Does not damage tissues

Drugs safer in pregnancy

If mother is hyperthyroid	If mother is hypothyroid
PTU (less potent than methimazole)	Dose of thyroxine is increases to 30-50% of previous dose as its volume of distribution increases
Recent advances: 1st trimester – PTU 2nd & 3rd trimester → Methimazole	

- TREATMENT /MANAGEMENT OF THYROID STORM
  - Thyroid storm (thyrotoxic crisis): This is an emergency due to decompensated hyperthyroidism. Vigorous treatment with the following is indicated:
  - **Nonselective beta blockers (e.g. propranolol) are the most valuable measure.** They afford dramatic symptomatic relief. In addition, higher doses reduce peripheral conversion of T_4 to T_3 Propranolol 1-2 mg slow i. v. may be followed by 40-80 mg oral every 6 hours. It may be withdrawn gradually when T_4 levels normalize.

- **Propylthiouracil 200-300 mg oral 6 hourly**: reduces hormone synthesis as well as peripheral T_4 to T_3 conversion. 4. 3.
- Iopanoic acid (0.5-1 g OD oral one hour after propylthiouracil) or ipodate are iodine containing radiocontrast media. They are potent inhibitors of thyroid hormone release from thyroid, as well as of peripheral T, to T conversion.
- **Corticosteroids (hydrocortisone 100 mg i. v. 8 hourly followed by oral prednisolone)**: help to tide over crisis, cover any adrenal insufficiency and reduce conversion of T_4 to T_3 in periphery.
- Diltiazem 60-120 mg BD oral may be added if tachycardia is not controlled by propranolol alone, or when it is contraindicated. Rehydration, anxiolytics, external cooling and appropriate antibiotics are the other measures.

CORTICOSTEROIDS

Steroids 00:00:10

- **Short acting**:
  - Cortisone → least potent agent
  - Hydrocortisone → Max Mineralocorticoid activity
- **Intermediate**:
  - Triamcinolone
  - Deflazacort → PO Duchene Muscular dystrophy
  - Flu prednisolone
  - Prednisone → Pro drug – is converted to Active form
  - Prednisolone → Prednisone is converted to Prednisolone in the body
- **Long acting**:
  - Dexamethasone } only glucocorticoid activity
  - Betamethasone
  - Paramethasone → Max Anti-inflammatory property
- **DE corticosterone Acetate**: → only Mineralocorticoid activity

Inhalational corticosteroids

- Budesonide
- Fluticasone
- Mometasone

- loc to route of administration → inhalational CS (of Couse mentioned in BA)

Other Uses:

- Replacement therapy – Cons. Adrenal hyperplasia
  - Adrenal in suffice

Uses: 00:03:10

- **Congenital Adrenal Hyperplasia(Dexa)**
- **Foetal lung maturity (Dexa/Beta)**
- Adrenal insufficiency
- Against Inflammations / Post- Transplantations
- Anti-Cancer agent (**except Kaposi sarcoma**)
- Eczematous skin diseases
- Bronchial Asthma

DOC TUTORIALS
LOGIN FOR SUCCESS

Adverse Drug Reactions of Glucocorticoids

00:04:31

Adverse Drug Reactions of Glucocorticoids

Short Term therapy < 14 days
↓
- Insomnia
- Hypomania
- Acute peptic ulcer

Long Term therapy > 14 days
↓
i. Erosion

- Rare: Acute Pancreatitis

Bone → avascular necrosis (MC is head of femur)

CI → osteoporosis

GI Mucosa

CI in PUD

ii. Decreases –

  a. height (causes dwarfism)

  b. Immunity

↓

CMI > Humoral Inhibits recruitment Of IL – 1 & 2

CI in Varicella, TB & Herpes

- Inflammation

↓

Release Annexins

↓

Inhibit PLA2

↓

Insulin

↓

CI in DM

↓

Potassium (Hypokalaemia)

↓

iii. Increases Pressure

↓

CI in HT & Glaucoma

Fluids → CI in CCF / RF

Increases Hair , Mood →
Psychoses
iv. Posterior subcapsular
Cataract
v. Epilepsy

Glucocorticoid Antagonistic Agents 00:09:43

Glucocorticoid Antagonistic agents

Receptor Antagonists
↓

i. Progesterone → antagonist, has anti glucocorticoid action.
ii. Selective Glucocorticoid Receptor modulators
e. g: Dagrocorat

Synthesis Inhibitors
↓

i. Abiraterone (blocks 17 α hydroxylase inhibits 17,20 lyase)
Abiraterone is currently Used for refractory
ii. Aminoglutethimide
iii. Mitotane
causes medical adrenalectomy
Carcinoma of Prostate

- How to taper Corticosteroids after 1Ong term use & why? HPA axis alteration
  - Suppression of hypothalamic-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy. In time, the adrenal cortex atrophies. Stoppage of exogenous steroid precipitates withdrawal syndrome consisting of malaise, fever,

anorexia, nausea, postural hypotension, electrolyte imbalance, weakness, pain in muscles and joints and reactivation of the disease for which the steroid was used. Subjected to stress, these patients may go into acute adrenal insufficiency leading to cardiovascular collapse.

- Any patient who has received > 20-25 mg day hydrocortisone, or 2 5 mg prednisolone day or equivalent for longer than 2-3 weeks should be put on a scheme of gradual withdrawal: 20 mg hydrocortisone/day reduction every week and then still smaller fractions once this level has been achieved. Such patients may need GH protection with a corticosteroid (oral or i. v) if a stressful situation develops up to one year after withdrawal. Administration of ACTH during withdrawal does not hasten recovery because it has been found that adrenals recover earlier than pituitary and hypothalamus.

DRUGS AFFECTING CALCIUM BALANCE -BASICS

- Drugs increases bone resorption (pharmacologically induced osteoporosis).

  Mnemonic: **EATLIPS**
- E → PGE_2
- A → alcoholism.
- T → thyroxine.
- L → loop diuretics.
- I → IL-1 & IL-6
- P → parathyroid hormone.
- S → steroids.

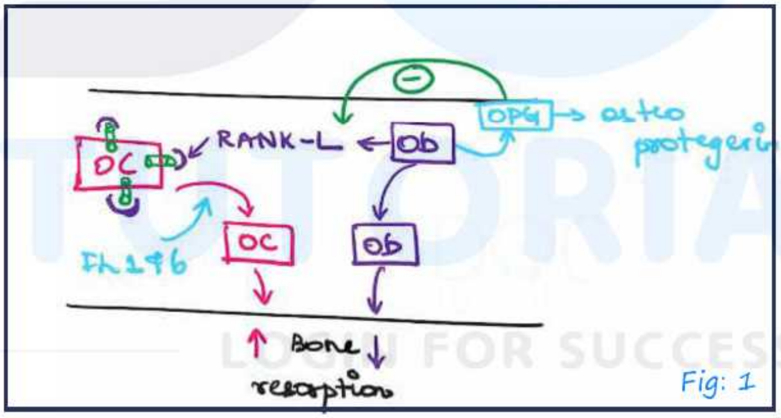

⊖
OPG → osteo protegerin
RANK-L
Ob
OC
OC
Ob
IL 1&6
↑ Bone ↓ resorption

Fig: 1

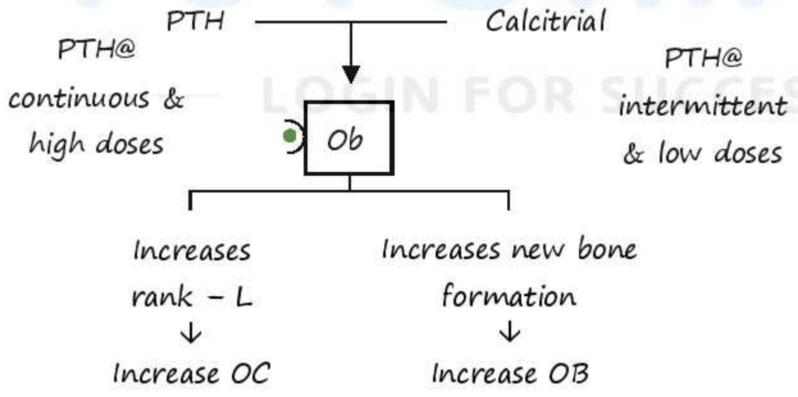
Drugs increasing bone resorption 00:01:19

- Osteoblasts → decrease bone resorption.
- Osteoclasts → increase bone resorption.
- Osteoblasts release RANK –L molecules.

- RANK –L sits on the osteoclasts → via IL1 & 6 osteoclasts are activated.
- Osteoblasts increase OPG (osteoprotegerin) molecules that in turn inhibit RANK –L.

Calcitonin 00:04:43

- Increases osteoblasts & inhibits osteoclast.
- Decreases serum calcium.
  i. PTH & calcitriol act on certain **receptors on osteoblasts → increase RANK –L → increase osteoclastic activity**
  (When PTH is given continuously at high closes)
  ii. PTH & calcitriol also cause increased new – bone formation (osteoblastic activity is more) → when PTH is given low doses and intermittently.


PTH
Calcitrial
PTH@
continuous &
high doses
PTH@
intermittent
& low doses
Ob
Increases
rank – L
↓
Increase OC
Increases new bone
formation
↓
Increase OB

CALCIUM AND PTH

Calcium in the treatment of bone related disorder

00:00:10

- Absorption
- Distribution
- Metabolism & Excretion

Absorption 00:00:24

- Facilitated diffusion & also by Active Transport

  Vitamin D dependent
- Absorption is decreased by
  - Phytates
  - Oxalates
  - Phosphates
  - tetracyclines
  - These drugs form complexes with calcium & prevents the calcium form getting absorbed which may lead to hypercalcemia. That's why tetracyclines tend to form bone and teeth deformities

Distribution 00:01:33

- **Ionized form of calcium** – active form of calcium
- Acidosis – Increase ionization
- Alkalosis – Decrease the ionization

Metabolism & excretion 00:01:46

- Reabsorption which is occurring
  - Reabsorption is increased by Vitamin D, Parathyroid hormone, Thiazide diuretics
  - If reabsorption is decreased more amount of calcium is excreted out of the body which means serum calcium is going to go low
  - Reabsorption is decreased by – Calcitonin

Preparations of calcium 00:03:40

- Carbonates →
  - Most common cause of flatulence among calcium products
  - To get absorbed it needs to interact HCL, it gets converted to absorbable form
  - So, any drug which is going to block HCL secretions is going to cause **hypocalcaemia** drugs like: –
  - PPI/ H_2RA/ elderly individuals
- Gluconate →
  - Given as iv route. It produces warmness locally. Can be used in the treatment of dermatosis, paraesthesia and weakness
- Lactate → given as per oral route
- Chloride → not be administered as a per oral route as it is a GI irritant

- All the calcium related products tends to have adverse effects like: - **bloating, constipation & flatulence**

Uses

- Tetany
- Osteoporosis
- Dietary supplement – in deficient states or in case of increased need like pregnancy & lactation
- Antacids

Parathyroid hormone 00:06:38

- It's a peptide molecule having short t½ - 2 - 5mins
- Its bone whenever it is given at continuous high doses. It in increases resorption
- When it is given at intermittent low doses it decreases resorption
- PTH - net effects: - **it increases serum calcium & it decreases serum phosphate**

CALCITONIN & VITAMIN D

- Parafollicular 'C' cells of thyroid

↓

Long Acting (8hrs)

↓

Resistance (usually not used > 2days)

Net effect → decreases the level of Serum Ca^{2+} and Serum PO_4^{3-}

Vitamin – D 00:01:14

VITAMIN D

Absorption
↓
Decreased by Cholestyramine and Liquid paraffin

Distribution
↓
Vit D binds with Vit D-R
↓
Increased Ca^{2+} reabsorption
Endocytic capture of Ca^{2++} In intestines. (increase)
Action on OC's and No Action on OB's
↓

Metabolism & Excretion
↓
Hydroxylation
$25(OH)D_3$ is longest acting agent

Increased
Resorption
Increased m-
RNA
transcription

Preparations of vitamin D 00:03:40

i. Alfacalcidol → 1α (OH) D_3 → Active form
  - will occur in liver
  - No need of kidney for activation
  - can be given by a PO route

ii. Calciferol → Natural Vit D_2

iii. Cholecalciferol → Vit D3

iv. Calcitriol → through PO route

v. Dihydro-tachysterol → synthetic Vit D_2
  - No need of kidney for activation

Uses of vitamin – D 00:05:39

i. Used in Vit D Deficiencies

ii. Hypoparathyroidism → DHT/ Alfacalcidol / Calcitriol

iii. Fanconi's

iv. Plaque Psoriasis → Calcipotriol (topical therapy)
↓
Non-Hypercalcaemic Vit D analogue

v. Metabolic rickets

Metabolic rickets

Vit D dependent	Vit D resistant	Renal
Rx: Calcitriol and alfa-Calcidol	Rx: PO_4^{3-} + Calcitriol / α Calcidol	Rx: α Calcidol / DHT

Treatment

Hypo-parathyroidism

↓

i. Vit D:
  - DHT / α Calcidol
  - PO route

ii. Teriparatide (SC route)
  - Recombinant PTH
  - more effective than Estrogen/ Bisphosphonates
  - Differentiate between Hypo / Pseudo hypo
  - Contra indicated in
    1 Hypercalcemia
    2 Paget's disease

Hyper-parathyroidism

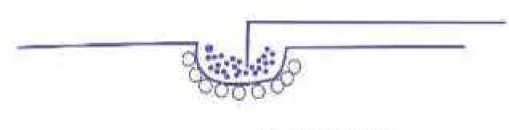
Rx: Cinacalcet

↓

Calcium sensitizer agent
- Ca^{2+} sensing receptors
- PO route
- Long-acting agent

BISPHOSPHONATES

- Uses to treat osteoporosis by breaking down osteoclasts and increasing activity of osteoblasts



Osteoclasts

↓

Bone

Ca^{+2} (Acidic)

↓

P-O-P binds with Ca^{+2}

↓

P-O-P endocytosed in osteoclasts

- Increases apoptosis
- Disrupts ruffled border of osteoclasts

- Blocks IL-6
- Inhibits differentiation of osteoclastic precursors

- Blocks mevalonate pathway
- Inhibits Farnesyl diphosphate synthesis
- Responsible for anti-tumor activity most commonly seen in Zoledronate

DOC TUTORIALS
LOGIN FOR SUCCESS

Route of administration 00:03:59

i. Routes of administration
  - Per-oral route
  - Parenteral

ii. Drugs given orally
  - Alendronate
  - Ibandronate
  - Risedronate

iii. Drugs given parenterally
  - Pamidronate
  - Zolendronate

iv. Drugs given orally have tendency to cause G.I irritation and GERD symptoms to prevent this few measures are taken like
  - Administered on empty stomach
  - Drink 1 glass of tap water with drug
  - Sit up right for 30 minutes after taking the drug

v. Parenteral drugs are long acting → therefore what is the frequency of administration.

vi. Pamidronate acts longer than Zolendronate

Uses of Bisphosphates 00:05:51

i. Osteoporosis

ii. Paget's disease

iii. Hypercalcemia of malignancy

iv. Osteolytic bone metastasis

i. PAMIDRONATE (given iv)
  - Adverse effects
  - Thrombophlebitis
  - Joint pain
  - Flulike symptoms (due to release of cytokines)

ii. **Alendronate** (given orally)
  - Oral Bioavailability is just 1%
  - Dose is reduced in renal failure
  - Elimination t1/2 is 10.5 years

iii. **Ibandronate** (given i.v/orally)
  - Decreases risk of vertebral fractures
  - Has no effect on any other kind of fracture

iv. **Zolendronate** (Given i.v)

- Given once a year for upto 5 years
- Adverse effects
- Renal toxicity
- Osteonecrosis of jaw (seen rarely at high closes)

Denosumab 00:08:59

- It's a monoclonal antibody
- It's an **inhibitor of RANK-L**
- It also blocks the bony metastasis in carcinoma breast, carcinoma prostate or bone loss due to gonadal suppression therapy
- Reduces risk of vertebral and hip fractures
- It is safe in renal failure
- Adverse Effects of Denosumab
- Dermatitis
- Initial hypocalcemia
- Hypersensitivity reactions
- **Increases susceptibility to infections**
- It can be given S.C **60mg/6months** (disadvantage compared to Zolendronate)
- Used for both male and female patients

Reverse Drug → Strontium Ranelate 00:13:04

- **It has tendency to increase risk of M.I and stroke**

Treatment of Hypercalcemia in malignancy

00:13:39

Treatment of hypercalcemia in malignancy

↓

Start with vigorous i.v saline

↓

Followed by i.v furosemide (Calciuria)

↓

i.v calcitonin for 2 days

↓

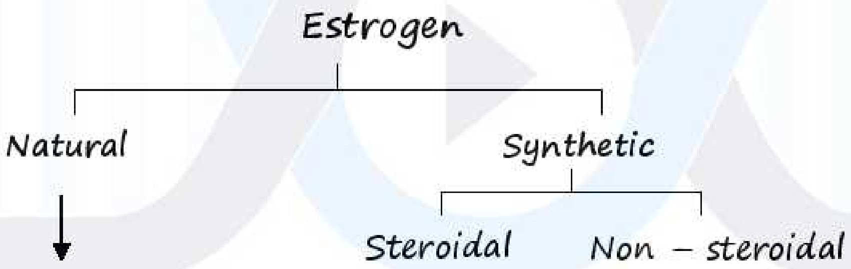
i.v pamidronate/Zoledronate will Ca^{+2} normalizes

AfraTafreeh.com TUTORIALS LOGIN FOR SUCCESS

SEX HORMONE – ESTROGEN, PROGESTINS AND OC

Estrogen 00:00:10

- In premenopausal women → Estrogen is secreted from ovarian theca, corpus luteum and placenta
- In postmenopausal women → Estrogen is secreted from adipose tissue, brain & liver
- Post-menopausal estrogen is derived from testosterone through aromatase enzyme



Estrone – Adipose tissue
Estradiol – Ovaries (most potent)
Estriol – Liver (Least potent)

- All the three types of estrogen have good P. O absorption and have high First Pass Metabolism
- Synthetic estrogens → steroidal
  - i. Ethinyl estradiol
  - ii. Mestranol
  - iii. Tibolone
- Non – Steroidal

i. DES

ii. Diene sterol

- DEC when administered to pregnant women increases the chances of cervical & vaginal adenocarcinoma in female babies

Adverse Drug Reactions of Estrogen

- Nausea & Vomiting
- Cause proliferation of breast, uterus & liver (Hepatic adenoma)
- CA uterus can be prevented by progestins
- Cholelithiasis
- Thrombosis
- DM/Edema
- Clomiphene is estrogen antagonist and is clearly classified under SERM

SERM (Selective Estrogen Receptor Modulators)

00:06:26

1.Clomiphene

- Antagonist action with hypothalamus

-RX: **Anovulatory infertility, Side effect - Multiple pregnancy**

2.Bazidoxifene (B)

3.Raloxifene (R)

4.Tamoxifen (T)

5.Toremefene

6.Doloxifene (D)

7.Ospemefene

- RX in Dyspareunia

8.Ormeloxifene

- Used as an OCP & in DUB
- Inhibits ovulation by producing utero embryonic asynchrony & implantation failure

- Breast
- Bone
- Lipid
- Uterus

(✓) ← BR → (X) Clot

- Breast
- Bone
- Lipid
- Uterus

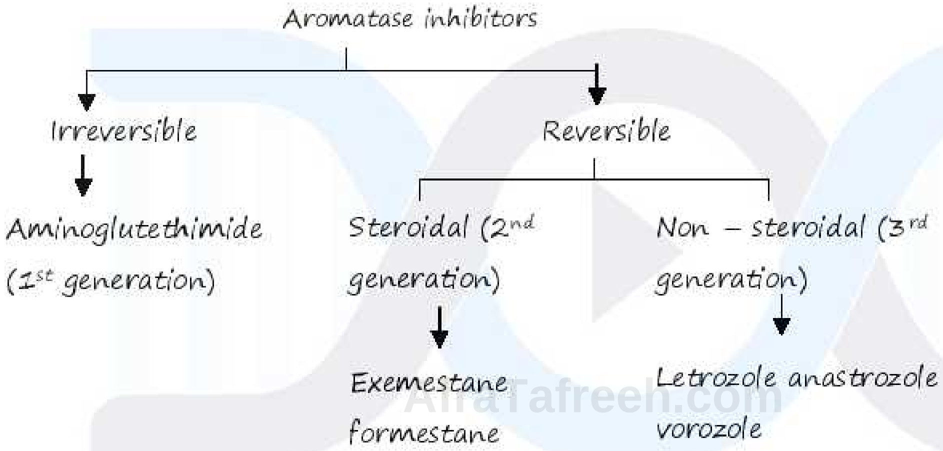
(✓) ← TD → (X) Clot uterus

SERD (Selective Estrogen Receptor Down Regulators) 00:11:42

- FULVESTRANT
- Estrogen antagonist
- Full action on vest → Therefore can be used for RX of Ca breast (tamoxifen resistant case) + Palbociclib (CDK inhibitor)

- IM route
- Safe, fast & long acting
- Adverse effects –
- Nausea asthenia hot flushes
- Headache

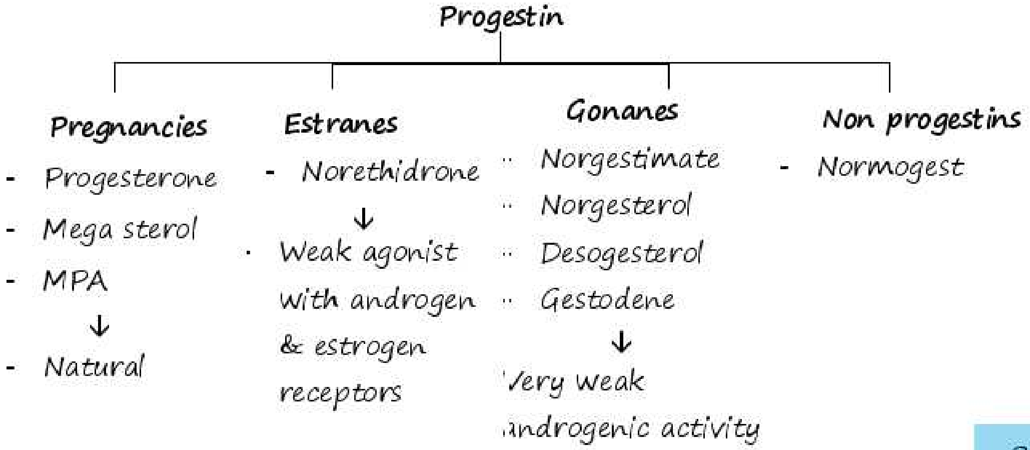
Estrogen synthesis inhibitors 00:14:12


Aromatase inhibitors
Irreversible
Reversible
Aminoglutethimide (1st generation)
Steroidal (2nd generation)
Non – steroidal (3rd generation)
Exemestane formestane
Letrozole anastrozole vorozole

DOT TUTORIALS
LOGIC FOR SUCCESS

- Uses: – Post Menopausal Ca breast
- Adverse effects: – Hot flushes, post-menopausal syndrome, Osteoporosis, Decreases HDL, increases LDL

Progesterone 00:16 :38


Progestin
Pregnancies
- Progesterone
- Mega sterol
- MPA
- Natural
Estranes
- Norethidrone
Weak agonist with androgen & estrogen receptors
Gonanes
Norgestimate
Norgesterol
Desogesterol
Gestodene
Very weak androgenic activity
Non progestins
- Normogest

SPRM (Selective Progesterone Receptor Modulators) 00:19:02

- Salient features
  - Inhibitor's ovulation
  - Anti-Proliferative effect on endometrium
  - Decreases uterine blood flow
  - Prevents Neovascularization

Drugs – Pris – Drugs

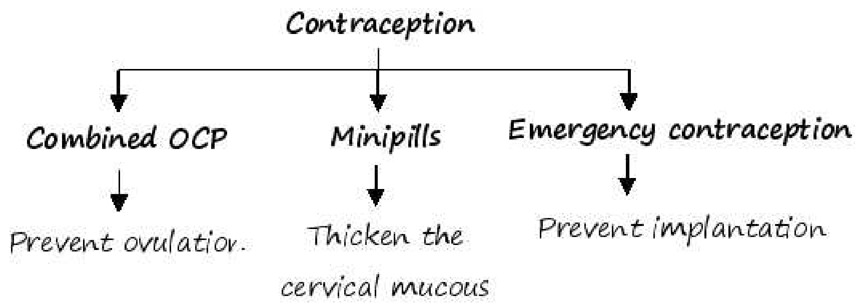
i. MIFEPRISTONE
- Both competitive & partial agonist
- Glucocorticoid & androgen receptor antagonist

ii. ULIPRISTAL
- Partial agonist
- Emergency contraception
- Treatment of fibroids
- Severe hepatotoxicity

iii. ONAPRISTONE
- Pure antagonist

iv. LILOPRISTONE– similar to mifepristone

Contraception 00:22:44


Contraception
Combined OCP
Minipills
Emergency contraception
Prevent ovulation.
Thicken the cervical mucous
Prevent implantation

Absolute CI for the use of contraception

00:24:00

Mnemonic: Pre-marital sex needs HELP

- Pressure (HTN)
- Malignancy
- Surgery
- Hepatoma
- Embolic events
- Lipid elevation
- Porphyria

Drug CI in porphyria

- **Barbiturates → Phenobarbitone in AIP**
- **O. C Pills**

Caution while using OC pills

Mnemonic: **Limited bed**

- Li → Liver Disease
- Mi → Migraine
- B → Bronchial asthma
- E → Epilepsy, Eye (Optic neuritis/Retrobulbar neuritis)
- D → DM

Emergency contraception 00:26:35

Mnemonic: DRINK MILO AFTER UNPROTECTED SEX

- **Mifepristone → Within 72hrs of unprotected sex**
- IUD → Within 72hrs of unprotected sex
- **Levonorgestrel → Within 5days of unprotected sex**
- OCP → **Within 72hrs of unprotected sex**
- **Ulipristal → Within 120hrs of unprotected sex**

SEX HORMONES – ANDROGENS

Androgens & its forms 00:00:43

- Major → Testosterone
- Active → DHT(most potent)
- Other → DHEA(least potent)
  - DHEA → Dehydroepiandrostenedione
  - Testosterone is converted to DHT by enzyme 5α – Reductase.
  - Testosterone can also be converted to estradiol by enzyme aromatase.
- Testosterone is responsible for: -
  - Development of internal Genitalia
  - Spermatogenesis
  - Inhibition of LH
- DHT is responsible for: -
  - Development of external genitalia
  - 2° sexual characteristics
  - Prostate Growth/Hypertrophy

Drugs targeting Androgens 00:03:36

Drugs targeting Androgens

Given orally (only 17 alkyl substituted)
↓
- Methyl testosterone
- Fluoxy testosterone

↓
Used to treat
- Hereditary angioneurotic edema
- Testicular failure
- Short stature
- Post-partum breast engorgement
- HIV wasting

Given parenterally
↓
- Testosterone undecanoate
- Testosterone propionate
- Testosterone Enanthate (longest acting)
- Testosterone isocaproate

↓
Used to treat
- Testicular failure
- HIV wasting
- Post-partum breast engorgement

ANABOLIC STEROIDS 00:05:40

i. Stanozolol
ii. Nandrolone
iii. Oxandrolone
iv. Oxymetholone
v. Methandienone

used for
- muscle wasting
- Anemia

- Adverse effects of Testosterone derivatives and Anabolic Steroids
- Mnemonic: 'HTML page in ANDROID'

H → Hydro testosterone
T→ Testicular atrophy
M→ Masculinization

L→ Liver(peliosis Hepatica)

Lipid (decreases HDL)

P → Polycythemia

A → Acne/Apnea

G → Gynecomastia

E → Edema

- "ANDROID" to remember these are androgen related.

DANAZOL (now replaced by GnRH agonists)

00:08:20

- Mechanism of action
  - i. Inhibits synthesis and release of pituitary Gonadotropins.
  - ii. Also has additional Androgenic/anti-estrogenic/anti progestogenic/anti-glucocorticoid effect.
  - iii. Decreases IgM, decreases IgA, decreases IgG.
- USES
  - i. Endometriosis
  - ii. fibroids
  - iii. Dysfunctional Uterine Bleeding
  - iv. Idiopathic Thrombocytopenic purpura
  - v. Hereditary angioneurotic edema.
- ADVERSE EFFECTS
  - i. Masculinization

ii. Hepatocellular damage

iii. Edema

Anti – Androgens 00:10:27

Anti – Androgens

- Synthesis inhibitors
  ↓
  - i. Ketoconazole
  - ii. Abiraterone
    ↓
    Used for
    - i. Castration resistant
    - ii. Ca – prostate
- 5α – reductase inhibitors
  ↓
  - 1. Finasteride
  - 2. Dutasteride
    ↓
    Used for
    - 1. BPH
    - 2. Male pattern
- Receptor antagonists
  ↓
  - i. Cyproterone
  - ii. Spironolactone
  - iii. Flutamide
  - iv. Niutamide
  - v. Enzalutamide
  - vi. Bicalutamide
    ↓
    Used for
    - 1. Ca prostate
      ↓
      Adverse effects
      - i. **Gynecomastia**
      - ii. **Hepatotoxicity (reversible)**

DOC TUTORIALS

- **Gossypol (derived from cotton seed) →inhibits spermatogenesis.**
  - Finasteride only blocks type 1 5α – reductase.
  - Dutasteride both type 1 and type 2 5α – reductase.

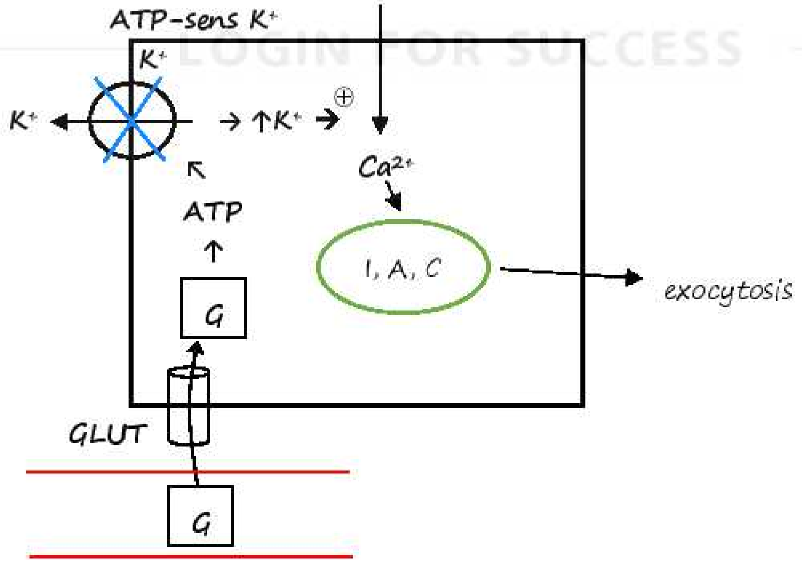
INSULIN AND ANALOGUES

Drugs used in treatment of diabetes mellitus

00:00:10

- Whenever there is increase in the blood sugar levels, the glucose present in the blood sugar levels moves into the beta cells with the help of a transporter called glucose transporter
- The glucose in the transporter cell is going to breakdown to form ATP
- K^+ channel is present on the surface of the beta cells (Efflux of potassium takes place through this channel)
- In beta cells increase in leads to blockage of K^+ channels thus these potassium channels are called as ATP sensitive potassium channels
- This leads to more accumulation of potassium

DOC TUTORIALS
LOGIN FOR SUCCESS



Insulin – decreases

- Decreases glycogenolysis
- Decreases gluconeogenesis
- Decreases lipolysis
- Decreases protein metabolism

It increases

- Glucose entry in muscle adipose tissue
- Glycolysis
- Glycogenesis
- Protein synthesis

Factors affecting insulin

- It is increased by vagal stimulation and β2 agonist
- It is decreases by somatostatin and α2 agonist

Recombinant forms of Insulin 00:05:30

- E. coli (PRB – Proinsulin recombinant bacterial)
- Yeast (PYR – Precursor Yeast Recombinant)
- Porcine (EMP – Enzymatic modification of porcine)

Drug interactions 00:06:33

- Drug interactions
  - Non selective β blockers Propranolol – Presents masking effect (Except in sweating)
  - Alcohol – cause more hypoglycemia

- Diuretics
- Steroids
- OCP
- Diazoxide

Hyperglycemia

Adverse effects 00:09:18

- Hypoglycemia (Treatment – Period (Iv-Glucose)
- Lipodystrophy
- Hypersensitivity reactions

less with newer recombinant once

- Edema

Types of insulin 00:09:58

a. Nasal – Afrezza – With basal insulin adverse effects – cough

- Contraindicated – smokers COPD & Bronchial asthma patients

b. Inhalation – faster onset, short acting

c. Parenteral → common route of administrations -SC

i. Rapid acting by IV route

- Lispro – Shortest acting parenteral insulin
- Aspart
- Glulisine – No zinc (Other contains zinc)

↓

Increases shelf life
Increases Stability

ii. Short acting by IV route

- Regular – Not mixed with lentils/Ultra anti-insulin
- All rapid & short acting are clear fluids

iii. Intermediate acting

- NPH/Isophane – Consists protamine
- Lente (Ultra – semi) (70:30)
- Both NPH & Lente are cloudy fluids

iv. Long acting

- Glargine – acidic drug (Not mixing with other drugs)
- Detemir
- Degludec – Longest acting (t ½ ~ 40hours)
- Ultra-lente
- Glargine determined in degludec are clear fluids whereas ultra-lentils is cloudy fluid

Insulin delivery devices 00:14:46

Insulin pen Fig: 1

Fig: 2 Insulin syringe

Fig: 3

- CSTI – Continuous subcutaneous insulin
- Through CSII - Only regular one fast acting

Fig: 4

- Nasal spray of insulin afrezza

Fig: 5

- Inhalation insulin – Shortest acting of all the devices

Fig: 6

- Artificial pancreas/Implantable pump
- It is of 2 different types – Mechanical/osmotic

NON-INSULIN ANTI-DIABETIC AGENTS

Non-Insulin Anti-Diabetic Agents: 00:00:05

Orla hypoglycemic agents (OAH)

- This is an old nomenclature
- All OHA are not given orally

  Ex: GLP-1 agonists → given SC

  Pramlintide → given SC
- All OHA doesn't cause Hypoglycemia, some maintain Normoglycemia

  Ex: PPAR gamma agonists (thiazolidinediones)

  So, now the nomenclature is changed to non-insulin Anti-diabetic drugs
- Treatment of type I DM

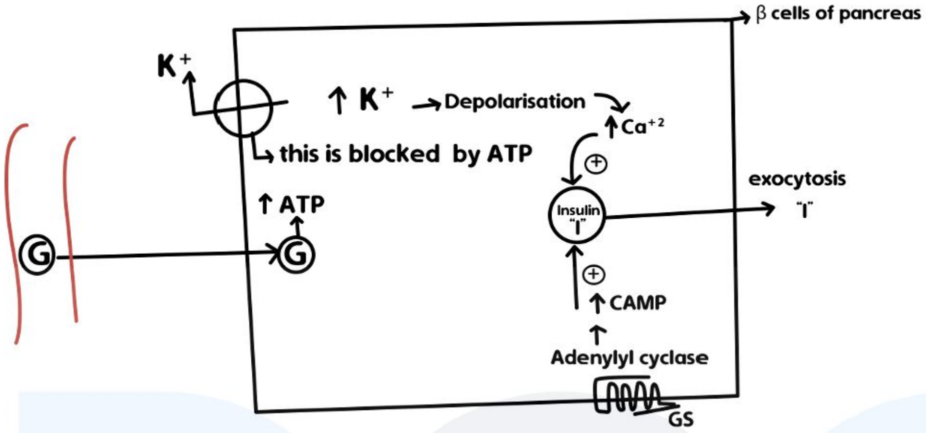
  i. Pramlintide -amylin analogue- given SC along with Insulin

  ii. Dapagliflozin (PO) first drug approved for PO in Type I DM

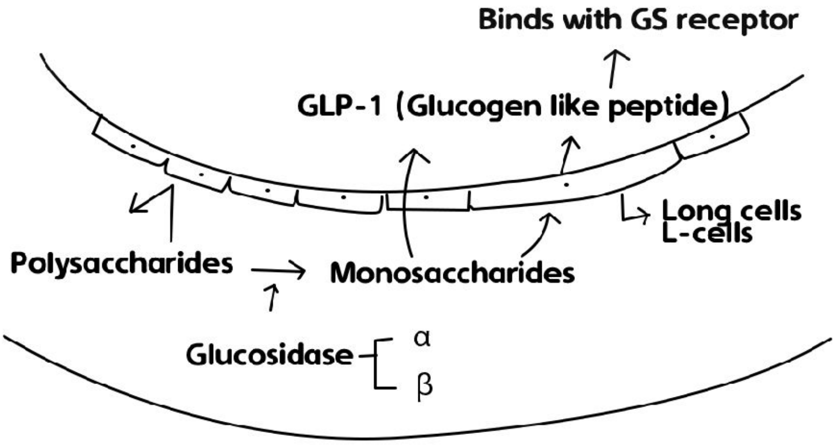
  iii. Sotaglifloxin (PO)

Mechanism of Action 00:03:30

- Normal physiology behind insulin Release: -


β cells of pancreas
K⁺
↑ K⁺
Depolarisation
↑ Ca⁺²
this is blocked by ATP
⊕
exocytosis
↑ ATP
Insulin "I"
"I"
G
G
⊕
↑ CAMP
Adenylyl cyclase
GS

- This exocytosis is induced by:
  - Increase in intracellular Ca^{+2}
  - Increase in intracellular CAMP
- Adenylyl cyclase (AC) converts ATP to CAMP
- Adenylyl cyclase levels are increased by GS receptors (surface receptor)
- Calcium moves into the cell only after depolarization


Binds with GS receptor
GLP-1 (Glucogen like peptide)
Long cells
L-cells
Polysaccharides
Monosaccharides
Glucosidase
α
β

- GLP-1 is broken down by DPP- IV

Sulphonyl urea's and meglitinides

- Sulphonyl ureas, meglitinides inhibit ATP-S-K^+ transporter and thereby increased K^+

Amylin analogues: -

- Ex: pr-Amlin-tide peptide molecule

Glucosidase enzyme inhibitors: -

- Acarbose
- Voglibose } more chance of development of flatulence
- Miglitol
- Flatulence may also seen in using:
  - Orlistat (anti-obesity)
  - Diloxanide furoate (anti- amoebic)

GLP_1 analogue:

- Exenatide
- Liraglutide

DPP4-4 inhibitors: - (-gliptins)

- Sitagliptin
- Vildagliptin

Other drugs

Metformin→ inhibits adenosine monophosphate kinase, inturn inhibits Hepatic & renal gluconeogenesis

- First drug of choice in treatment of Type II DM

Thiazolidinediones→ PPAR gamma agonist

SGLT-2 inhibitors- (-glifloxins)

- SGLT-2 transporter present in nephrons reabsorb glucose, Na+.

  if this is blocked then glucose excretion is more thus decreasing blood glucose

  gli→ glucose inhibitor agents
- Can cause UTI

Insulin secretagogues 00:19:00

Sulphonyl urea's

↓

- More potent
- Long acting

↓

Maintenance therapy for T2DM

Meglitinides

↓

- Less potent
- Short acting
- Ex: Nateglinide, repaglinide

↓

Used for Postprandial Hyperglycemia

- There must be functional β-cell reserve of ≥ 30%
- These tend to produce

  i. Hypoglycemia

  ↓

  Treatment – Glucogon

ii. Weight gain

Classification of sulphonyl ureas 00:23:30

Short acting	Intermediate acting	Long acting
↓ Tolbutamide ↓ Safest sulphonyl urea in renal failure ↓ Has dermatological, GI adverse effects	• Acetohexamide – uricosuric • Tolazamide – mild diuretic • Glipizide – Safe in elderly – Less hypoglycemia high PPB • Glibenclamide – max potency – Mild diuretic • Gliclazide – Anti-platelet	↓ • Chlorpropamide • Most hypoglycemia, dilution hypo Na^+ • Glimepiride ↓ Extensively reabsorbed

Biguanides: 00:28:05

Metformin

- Inhibit adenosine monophosphate kinase

  ↓

  Inhibit Hepatic, Renal gluconeogenesis
- Decrease insulin resistance
- Decrease LDL

- Delays gastric emptying – weight neutral activity

↓

Accentuated by increase leptin, increase insulin sensitivity of hypothalamus

- Insulin sparing effects
- Safer in children (other -liraglutide)
- Can be used for PCOD, non-Alcoholic steato-hepatitis
- Anti-ageing property

Adverse Effects of over use of metformin:

- Most common -nausea, abdominal cramps, Diarrhea
- Vitamin B12 deficiency – treatment – Ca+2 supplements
- Lactic acidosis – in Renal liver failure
  - Alcoholics
  - Chronic CPD

Metformin + digoxin/ Ranitidine causes lactic acidosis

- Contraindicated in Renal failure
  - If eGFR < 30ml/min
  - If eGFR > 45 ml/min – then safe

Thiazolidinediones 00:38:30

- PPAR gamma agonist
  ↓
  Increase insulin Receptors synthesis
  ↓
  Increased Insulin sensitivity
  ↓
  No hypoglycemia - safe in Renal failure

Ex:

- Pioglitazone
- Rosiglitazone
- Troglitazone

Adverse effects

- Edema
  - Increase CCF
  - Weight gain
  - Macular edema – treatment - discontinue drug
- Increased risk of fractures in females

α- Glucosidase (α-G) Inhibitors: - 00:41:50

- Doesn't produce hypoglycemia except miglitol
  ↓
  (Might cause Hypoglycemia)
- Acarbose
- Voglibose

Acarbose, Voglibose – Inhibitors α-G; α-amylase

- Miglitol- inhibit α & β-G

- Administered after 1st bite of meal

Adverse effects: -

  - Flatulence
  - If produce hypoglycemia treatment - monosaccharides PO

GLP-1 analogues 00:47:05

- Exenatide
- Liraglutide } given SC
- Albiglutide
- Liraglutide – may produce weight loss (treatment for obesity)
  - Teduglutide- GLP-2 analogue
  - Semaglutide – PO
- Contraindicated in MEN II & Medullary Thyroid Ca
- Most common – nausea, vomiting, Diarrhea
- Some may develop acute pancreatitis

DPP-IV inhibitor 00:49:40

ACE- a.k.a Peptidyl di peptidase, Kininase – II

- DPP-IV breaks down GLP-1

GLP (Glucose dependent insulinotropic peptide)

- Gliptin → peptidase inhibitors
- Sitagliptin → increased β-cell function

- Saxagliptin } → CCF
- Alogliptin }
- Linagliptin – safe in Renal failure (∴ Bile excretion)
- Vildagliptin – Hepatitis
- Teneligliptin

Adverse effects:

- Headache
- URTI
- Pancreatitis (Sita > Lina)

Amylin analogues 00:55:05

- Pr- Amlin-tide

  ↓

  - Short duration of action
  - SC – subcutaneous
  - Given Just before meals
  - Given along with insulin

    ↓

    Dose of Insulin decreased by 50% of previous value

    - should be given in separate syringes

SGLT-2 Inhibitor 00:57:15

- It is in PCT; involved in reabsorption of glucose
- Gli flozin → urinary flow

  Ex: i. canagliflozin

  ii. Dapagliflozin→ Approved by EMA for T1 & T2 DM

- Sotagliflozin → Approved by FDA for T1 & T2 DM
  → SGLT – 1&2 inhibitor
- Ertugliflozin
- Empagliflozin

Adverse effects:

- More chances of UTI
- Osteoporosis
- Hypotension
- DKA
- Fournier's gangrene (least common with Ertu, Empa)

Newer Drugs 01:00:30

- Bromocriptine– Administrated early morning within three hours of awakening
- Colesevelam
- Saroglitazar – Dual PPAR α + PPAR gamma agonists

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Antidiabetic altering body weight

Increased	Unchanged	Decreased
• Sulphonyl urea's • Insulin • Thiazolidinediones	• Metformin • α-G – inhibitor • DDP – 4 inhibitors	• GLP-1 analogue • Pramlintide • SGLT-2 inhibitor

HISTAMINE

It is a mediator of -

- Inflammation
- Anaphylaxis
- Gastric acid secretion
- Neurotransmitter

Synthesis: -

- Synthesized from histidine

↓ Decarboxylation

Histamine

n-methyl transferase | Di amino Oxidase

N – Methyl Histamine | Imidazole acetic acid

↓ Monoamine oxidase B

Excreted in Urine (as inactive metabolite)

Release 00:05:00

Stored in

Mnemonic
[mast cell granules causes media expansion]

Mast cells
↓
Degranulation
↓
Seen in immediate hypersensitivity reaction:
- Phospholipase A_2
- Tyrosine kinase

Non mast cells
↓
Displacement
↓
Drug induced release (i.e., histamine liberators)
M – Morphine
A – Amine Antibiotics
S – Succinyl choline, sting of wasp

T – Tubocurarine
G – Guanithidine
Media – Radio contrast media
expansion – Plasma expanders
vancomycin – causes histamine and cytokinin release (Red Person Syndrome)

Receptors of histamine 00:08:50

All are GPCR

$H_1 \rightarrow G_q$

$H_2 \rightarrow G_s$

$\left.\begin{array}{l} H_3 \\ H_4 \end{array}\right\}$ Gi/o → Block actions of histamine

Actions 00:09:50

1.GIT: Increase smooth muscle contraction
Increase gastric acid secretion

2.Blood vessels:

Small blood vessels → Dilated
Large blood vessels → constricted
} Overall decrease BP (Dilatation of resistance vessels)

Note:

Hypotension caused by histamine lasts longer than acetylcholine

Since, acetylcholine esterase is fast acting and it will degrade Ach

3.Skin: Red → Reddening

Wheal → Swelling

Flare → Flushing

4.Extravascular smooth muscle → H_1 → Bronchoconstriction

(Bronchial smooth muscle) (But this is dominant)

H_2 → Broncho dilatation

5. CNS → induce wakefulness

Decrease Appetite

Note:

Awake Neurotransmitter : Histamine & Orexin

→ Eg: SUVOREXANT – sedation/hypnosis

↓

Orexin Antagonist

Adverse effects: Depression

Histamine agonistic agents 00:16:50

- Histamine
- Betahistine → used in vertigo
- Impromidine
- Methemepip

Histamine antagonists / Blockers 00:17:39

H_1 Blockers

1st Generation

Highly Sedative

1. Diphenhydramine
2. Dimenhydrinate
3. Promethazine
4. Hydroxyzine

Moderately Sedative

1. Pheniramine
2. Cyproheptadine
3. Meclizine
4. Buclizine
5. Cinnarizine

Mild Sedative

1. Chlorphenamine
2. Dexchlorpheniramine
3. Dimethindene
4. Triprolidine
5. Cyclizine
6. Clemastines

2nd Generation

1. Loratadine
2. Cetirizine
3. Azelastine
4. Mizolastine
5. Ebastine
6. Rupatadine
7. Olopatadine
8. alcaftadine

3rd Generation

1. Deslorantidine
2. levocetirizine
3. fexofenadine

Note:

		Except
All – Dine Tine Rizine	Are 2nd generation	Cyproheptadine, riprolidine clemastine cinnarizine

All – amines
Lizines
Are 1st generation

Antihistamines 00:20:50

With anti-cholinergic property
↓
- Promethazine
- Diphenhydramine

Uses

1. Acute dystonia
2. Drug induced parkinsonism
3. Motion sickness

With local anaesthetic property
- Promethazine
- Dimenhydrinate

↓
Tend to block Na+ channels in excitable tissue

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Pharmacokinetics 00:28:20

- Terfenadine, Astemizole – Produce torse de pointes – therefore Banned

↓↓

These metabolized by cytochrome P enzymes
Therefore, if CYP enzyme inhibitors present
Increase risk of torse de pointes with these drugs

- Fexofenadine derived from terfenadine → do not produce torse de pointes
  since, it is excreted unchanged in Faeces

- Note
  - Excreted Unchanged In urine
    - C – Cetirizine
    - L – Cortisone

    F – Fexofenadine – excreted unchanged in faeces

- Antihistaminic
- Anti-cholinergic
- Anti-serotonergic → stimulate appetite

Eg: Cyproheptadine

- Anticholinergic
- Anti-serotonergic
- Vasodilatory properties → since, it blocks ca^{2+} influx.

Eg: Cinnarizine

- Anticholinergic
- Antiemetic
- Weak α Blockade postural hypotension
- Local anesthetic action

Eg: Promethazine

- Poor CNS penetration
- No anticholinergic property
- Long acting

Loratidine

- Active metabolite of loratidine
- High affinity with H1

Desloratadine

- Dose dependent sedation – Fexofenadine

- Inhibit histamine release, leukotrienes
- Maximum topical activity
- Causes bronchodilation
- Given intranasally

Azelastine

- Metabolite of hydroxyzine
- No cardiac effect
- Less sedation

cetrizine

- No use in motion sickness / emesis

- Additional platelet activating factor
- Antagonist property
- Used for allergic rhinitis

Rupatadine

Pregnancy 00:32:50

Contraindicated	Indicated
Azelastine	CPM
Hydroxyzine	Cetrizine
Fexofenadine	Loratadine

H_2 Antagonistic Agents 00:33:44

- These drugs decrease gastric acid secretion

Eg: - cimetidine
- Ranitidine
- Famotidine
- Nizatidine = 100% per oral bioavailability

H_3 Receptors 00:34:53

- H_3 inverse agonists: Produce wakefulness

  Thioperamide

  Clobenpropit

  Tiprolisant → Therefore used for narcolepsy

- H_3 Inverse agonist
- H_4 Inverse agonist

  ] Thioperamide

- H_3 Inverse agonist
- H_4 partial agonist

  ] Clobenpropit

- H_3 agonist
- H_4 Antagonist

  ] Impentamine

- H_3 Inverse agonist
- H_4 Antagonist

  ] Iodophenpropit

HISTAMINE PART – III

(DRUGS FOR MOTION SICKNESS)

Motion Sickness

Drug	Indication	Dosage	How to use	Adverse Effect
Anti-Cholinergic:				
Scopolamine	Sea and travel sickness	Transdermal 1.5 mg/ patch	Prevention: 6-8h before exposure Effective for 72 hrs.	Dry eyes, mouth mydriasis with light sensitivity Rare: Glaucoma Cataract, dermatitis unilateral mydriasis
Antihistamines:				
Cinnarizine +	Vertigo	Cinnarizine 20mg	Acute treatment only	Drowsiness,

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Dimenhydrinate		Dimenhydrinate 40mg	TDS for 4 weeks	headache, Rare: Urinary retention, paraesthesia, amnesia, sweating, tinnitus
Dimenhydrinate	Nausea and vomiting motion sickness	50-100mg OD CI < 3yrs Dose reduced in children	Prevention: 0.5 – 1 hr before start of travel	Somnolence, drowsiness
Diphenhydramine	Nausea, vomiting, sleep disturbances	50 mg/day CI < 18 yrs	Short term therapy: 30 min before sleep	Addiction, tolerance development, drowsiness,

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				muscle weakness
Promethazine	Nausea and vomiting	20-30 mg starting dose Can be given in children >2yrs of age	Reserve Drug	Sedation, anti-cholinergic side effects

SEROTONIN

Serotonin 00:01:19

- It is called happy hormone

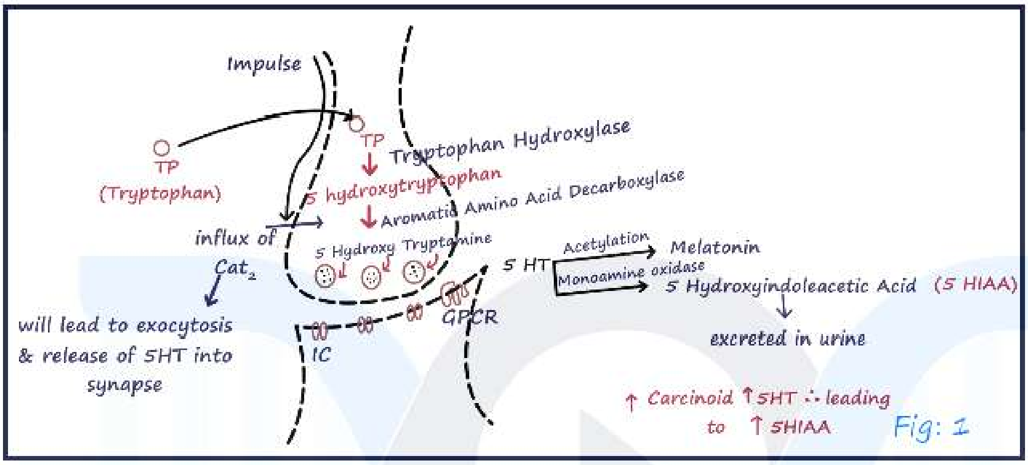
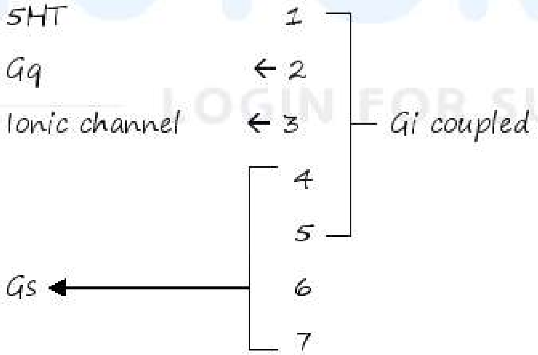

Impulse
TP
(Tryptophan)
TP
Tryptophan Hydroxylase
5 hydroxytryptophan
Aromatic Amino Acid Decarboxylase
5 Hydroxy Tryptamine
influx of
Ca^{+}_{2}
will lead to exocytosis
& release of 5HT into
synapse
IC
GPCR
5 HT
Acetylation
Melatonin
Monoamine oxidase
5 Hydroxyindoleacetic Acid (5 HIAA)
excreted in urine
↑ Carcinoid ↑ 5HT ∴ leading
to ↑ 5HIAA

Fig: 1

Receptors 00:07:10

- 14 types of serotonin receptors

  7 are major


5HT
1
Gq
← 2
Ionic channel
← 3
Gi coupled
4
5
Gs
6
7

Receptor and its location 00:09:24

- 5HT₁: 1A 1B 1D 1E 1F

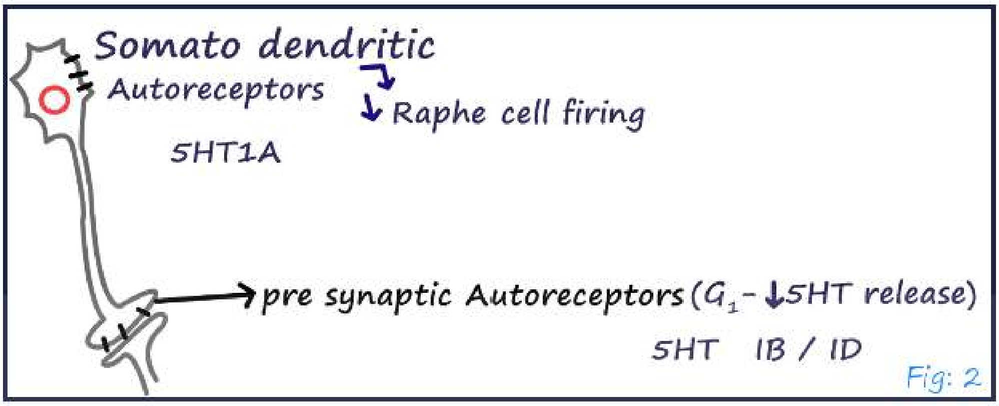

Somato dendritic
Autoreceptors
5HT1A
↓ Raphe cell firing
pre synaptic Autoreceptors (G_1 - ↓5HT release)
5HT IB / ID

Fig: 2

- 5HT₂: 2A 2B 2C
  (Gq)
  - 2A ↓
    - CNS
    - Platelets
    - Smooth muscles
  - 2C ↓
    - Choroidal plexus → induce CSF production
    - Involved in reduction of appetite

- 5HT₃: Location: area prostrema (CNS) | Induce emesis
  (Ionic) Parasympathetic terminals of GIT
  Fast acting

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- 5HT₄:

GIT Hippocampus	Increase GI motility Increase secretion	Therefore, used in constipation

Drug classification 00:17:10

5HT$_{1A}$	5HT 1B/1D	5HT$_{2A/2C}$	5HT$_3$	5HT$_4$
Partial agonist ↓ • One Eg: Buspirone Gepirone Iperpirone Vilazodone ↓ • Anxiety • Depression	BAD "Agonist" / TRIP • Triptan ↓ Suma triptan Nara triptan ↓ Treatment: Migraine	agonist ↓ Ketanserein Risperidone Methy sergide Clozapine ↓ Treatment: • Migraine • Depression • Psychosis	agonist ↓ • Threeon / tron ondanssethreeon grani sethreeon tropisethreeons palanoosethroeon ↓ Treatment: Antiemesis Doc for chemotherapy induced emeris	agonistic ↓ • Ride cisapride Mosapride tegaserod (Banned) prucalopride ↓ increase GI motility

Note: Doc for prophylaxis of migraine: Propranolol

Agonists 00:23:44

1. Triptans: - Produce vasoconstriction of intracranial blood vessels

(5HI 1B/1D) including arteria venous anastomosis

↓

Closing shunts

↓

Restores blood flows

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Adverse drug effects

- common
  - via S/C route: Irritation
  - per oral: Paresthesia
    - Fatigue
    - chest tightness
    - drowsiness
- rare
  - Coronary artery vasosparm
  - Transient MI

Contraindications

- Uncontrolled hypertension
- Renal diseases → Naratriptan contraindicated
- Hepatic disease → eletriptan contraindicated
- In patients with prior exposure to ergot. Since risk of MI increases
  ↓
  Cause vasoconstriction

Pharmaco kinetics

Oral Bioavailability

- Maximum ↓ Naratriptan
- Minimum ↓ Sumatriptan
  Therefore, given via s/c route

Duration of action

- Maximum ↓ Frovatriptan
- Minimum ↓ Sumatriptan
  Therefore, not given for maintainanence therapy

Onset of action

- Faster: Rizatriptan
- Slower: Frovatriptan

Plasma protein binding

- Maximum ↓ Eletriptan
- Minimum ↓ Sumatriptan

2.Methysergide

- It is an ergot derivative, it has $5HT_1$ → agonist
  $5HT_{2A/2C}$ → Antagonist

  Was previously used for prophylaxis of migraine, now not used since produce fibrosis (Pleuro pulmonary) now propranolol is used.

Note: all ergot alkaloids and their derivatives tend to produce vasospasm and fibrosis ↓

Methysergide
Bromocriptine
Cabergoline

Drugs producing pulmonary fibrosis

Mnemonic: "NICE BABE"

NI – Nitrofurantoin
CE – Cyclophosphamide
B – Busulfan
A – amiodarone
B – Bleomycin
E – Ergot and its derivatives

3.Lysergic acid diethylamine (LSD)

- Universal agonistic property
- It is hallucinogen ($5HT_{1A}$ agonistic property)

4.Buspirone:

- $5HT_{1A}$ receptor
  - Presynaptic area → Full agonist
  - Post synaptic area → partial agonist

- Delayed onset of action
- Actions are similar to GABA

5.Lor caserine:

$5HT_2$ agonist
↓
Weight loss

Now not used because of inefficacy and adverse effects

6.Flibanserine

$5HT_{1A}$ agonist
$5HT_2$ agonist
– Used in hypoactive sexual desire disorder

7.Vilazodone:

Have selective serotonin reuptake inhibitors

$5HT_{1A}$ partial agonist

Treatment: Major depressive disorder

Antagonistic agents 00:40:45

1.Ketanserin:

- Acts as antagonistic agent
  - $5HT_{2A}$
  - $5HT_{2c}$

  – Inhibit platelet aggregation
  - H_1 → Sedation
  - α_1 → postural hypotension decrease BP
- Ritanserin – selective for 5HT 2A/2C receptor

2.Cyproheptadine: Antagonist Drug at

- 5HT2A →

  i. Induce appetite

  ii. Post gastrectomy dumping syndrome

- H1 →

  iii. Intestinal hypomotility in carcinoid
- Muscarnic receptors

3.Settrons

- Grani
- Ondan
- Dola → QT prolongation
- ALO → No antiemetic properly – used for IBD with diarrhoea
- Palono → Doc for chemotherapy induced emeris (CIE)
- CIE
  - Early: Doc $5HT_3$ antagonist – palonosetron
  - Delayed: NK_1 receptor antagonist – Netupitant

Ergot alkaloids 00:47:20

Partial agonist

↓

α 5HT

↓

Used for demonstration of vasomotor reversal of dale.

Full agonist

↓

D_2 receptors

Ergot

Vessels

↓

Ergotamine

↓

Vasoconstriction

↓

Over dose

- Ischemia
- Gangrene
  can produce fibrosis
- Can be used for migraine
- Caffeine is combined with ergot
  since, it increases absorption of ergot

↓↓

Tend to produce cumulative toxicity

Uterus

↓

Ergometrine / ergonovine

- Produce uterine contraction

↓

Pregnant uterus more contrition, especially at term

↓

since, uterine contraction& vasoconstriction

↓

Can be used in PPH.

CNS

↓

ergotoxin

- Powerful hallucinogen

↓↓

dihydroergotoxin

↓

used in treatment of dementia

not used now.

since cause pleuropulmonary fibrosis

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Hydrogenation 00:56:00

- Decrease α agonistic property
- Increase α antagonistic property

Adverse effects

- Most common: Nausea / vomiting / Diarrhoea
- Other: Gangrene of extremities

Clinical:

- Pregnant women
- Peripheral vascular disease
- Coronary artery disease
- Hypertension
- Impaired hepatic / Renal function which might lead to cumulative toxicity
- Within 24 hours of use of triptans

SEROTONIN PART – III (DRUGS FOR MIGRAINE)

Treatment of Migraine 00:00:10

Acute Migraine

i. Rest in a quiet darkened room.

ii. Administer simple analgesics (not more than 15 days/month).

iii. Combination analgesics (not more than 10 days/month).

iv. Ergotamine tartrate (1mg) + caffeine (100mg) can be administered by per oral route or per rectal route.

- It is contraindicated in:
  - Pregnancy
  - Heart disease
  - CYP3A4 inhibitors.

v. Triptans:

- Sumatriptan is administered subcutaneously.
- Nasal/per oral **Sumatriptan** is given but it is less effective due to poor absorption.
- Nasal/per oral **Zolmitriptan** is a newer drug.
- Eletriptan.
- This day is contraindicated in:
  - Pregnancy
  - Hemiplegic/basilar migraine

- Coronary/peripheral vascular disorders
- History of stroke
- TIA
- Uncontrolled hypertension

vi. Other days:

- Prochlorperazine – it can be given per rectal/I.V/I.M.
- Opioid analgesics are avoided as it might cause rebound headache.

Chronic Migraine 00:03:35

1.Antiepileptics are given by per oral route -

- Topiramate [tends to cause weight loss]
- Gabapentin
- Valproic acid

Causes weight gain

2.Anti-depressants are given by per oral route -

- Amitriptyline.
- Venlafaxine

3.Antihistaminic are given by per oral route -

- Flunarizine.
- cyproheptadine.

4.Alpha agonists is given by per oral route -

- Clonidine

5.Beta blockers are given by per oral route-

- Propranolol (DOC)
- Atenolol.
- Metoprolol.
- Nadolol.
- Timolol.

6.Calcium channel blockers is given by per oral route-

- Verapamil

7.Anti CGRP monodonal antibodies are given by subcutaneous route as they are long acting and can be given once a month-

- Erenumab.
- Framenezumab.
- Galcanezumab

8. Other drugs are-

- Botulinum toxcin A which is given by intra muscular route.
- Riboflavin is given by per oral route.

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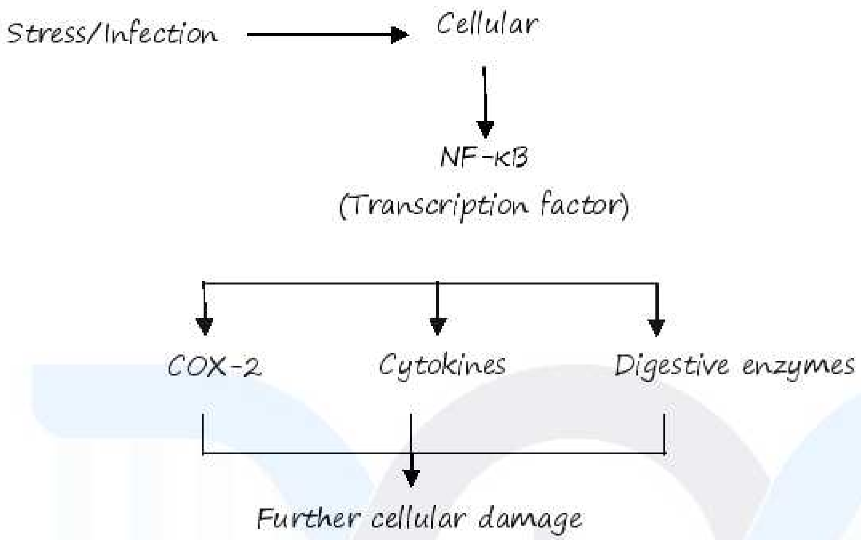
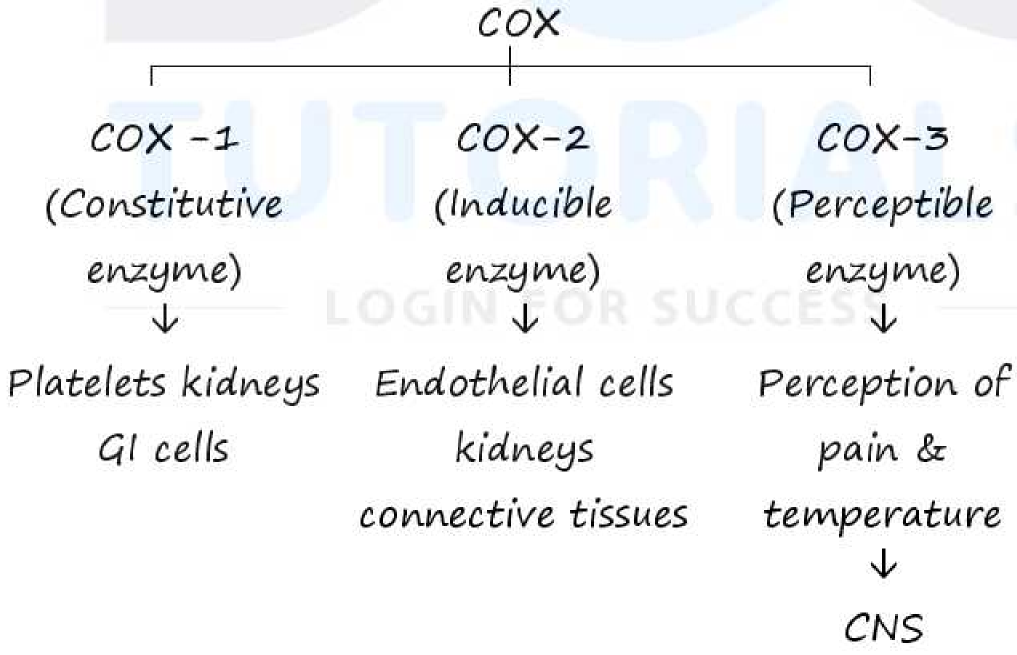
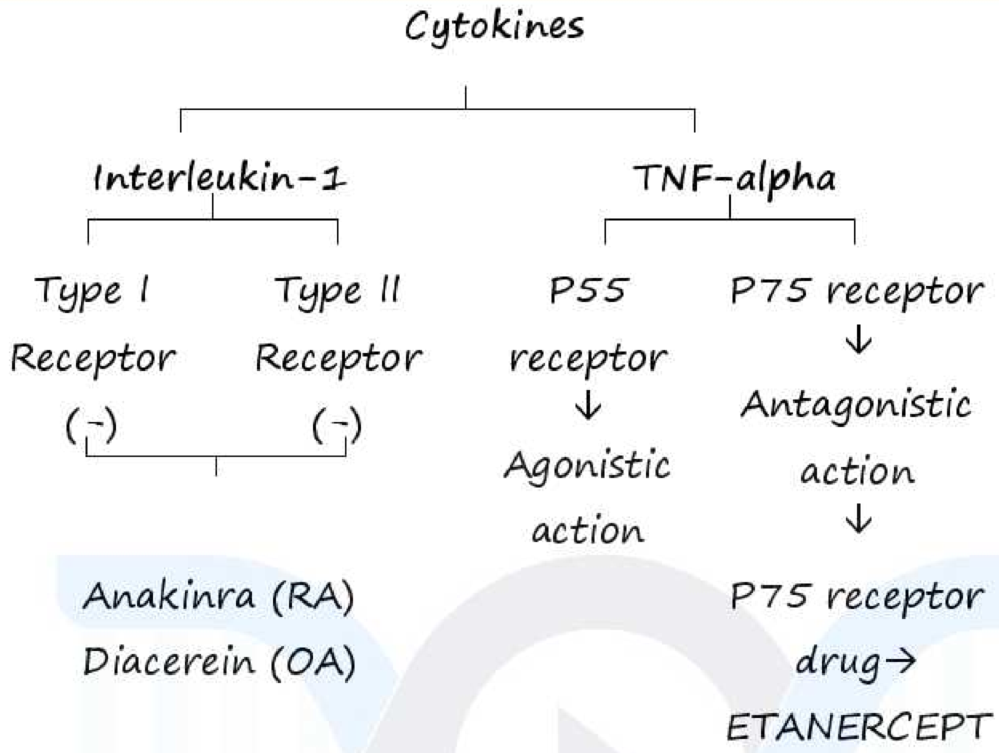
PROSTAGLANDINS PART – I

Prostaglandins 00:00:10


Stress/Infection
Cellular
NF-κB
(Transcription factor)
COX-2
Cytokines
Digestive enzymes
Further cellular damage

COX enzymes 00:04:40


COX
COX -1
(Constitutive enzyme)
Platelets kidneys
GI cells
COX-2
(Inducible enzyme)
Endothelial cells
kidneys
connective tissues
COX-3
(Perceptible enzyme)
Perception of pain & temperature
CNS



Cytokines

Interleukin-1

Type I Receptor (-)

Type II Receptor (-)

Anakinra (RA)

Diacerein (OA)

TNF-alpha

P55 receptor → Agonistic action

P75 receptor → Antagonistic action → P75 receptor drug → ETANERCEPT

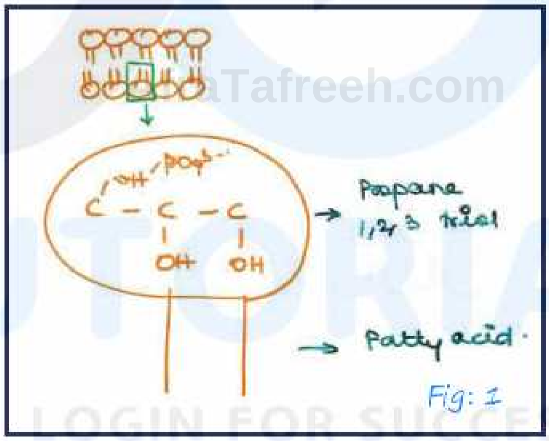
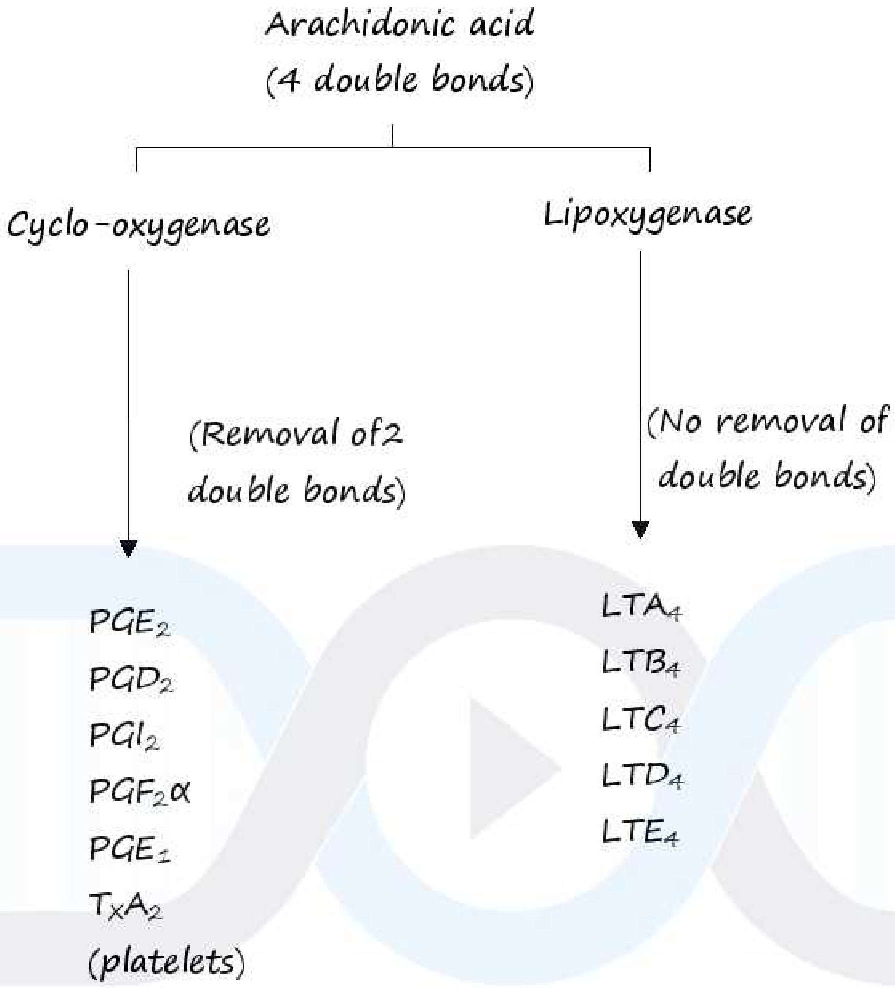


Fig: 1

- Fatty acid along with the ester bond is cleaved from the lipoprotein molecule the resultant compound is called **ARACHIDONIC ACID**
- Phospholipase A_2 is the enzyme that cleaves arachidonic acid from the lipoprotein molecule
- Arachidonic acid has 4 double bonds → Tetraenoic acid

PG_3 and LT_3 00:07:20



Arachidonic acid
(4 double bonds)

Cyclo-oxygenase

(Removal of 2 double bonds)

PGE_2
PGD_2
PGI_2
$PGF_{2}\alpha$
PGE_1
T_XA_2 (platelets)

Lipoxygenase

(No removal of double bonds)

LTA_4
LTB_4
LTC_4
LTD_4
LTE_4

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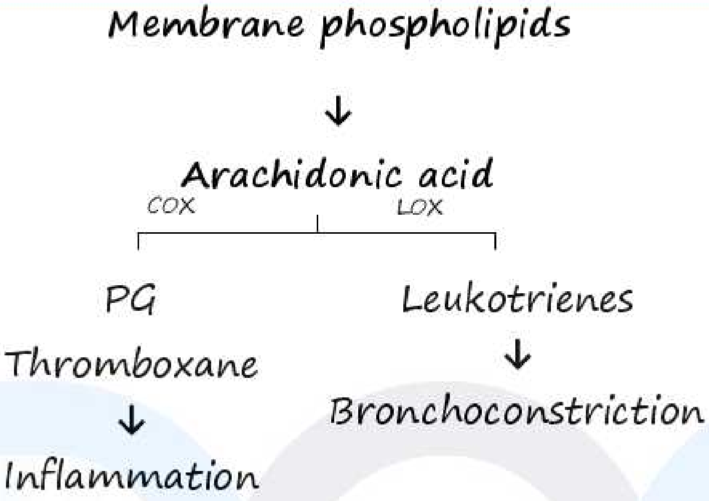
PROSTAGLANDINS PART-II

COX inhibitors 00:01:00


Membrane phospholipids
Arachidonic acid
COX
LOX
PG
Thromboxane
Inflammation
Leukotrienes
Bronchoconstriction

- Cyclooxygenase enzyme is inhibited by aspirin and each other NSAID's
- Aspirin is an irreversible inhibitor
- Lipoxygenase enzyme is inhibited by Zileuton
- **Phospholipase A_2 can be inhibited by steroids**
- Licofelone inhibits both cyclooxygenase and lipoxygenase enzyme
- Licofelone is used for osteoarthritis

Types of prostaglandins 00:06:00

PGE_1	PGE_2	PGI_2	F_2 Alpha
A	A	A	P
B D	B d	P D	U C
V ↓ • Acid secretion Decreased • Broncho dilatation • Vasodilatation	V FDA & PUC ↓ • Acid secretion deceased • Broncho-dilatation • Vaso-dilatation • Fever • Ductus Arteriosus (patient) (E_1 & E_2 & I_2) • Pain • Uterine contraction • Cervical ripening	V PDA ↓ • Acid Secretion Decreased • Platelet aggregation Decreased • VD (vasodilation) potent • Pain • Ductus Arteriosus (Patent)	B ↓ • Pupillary Constriction • Uterine Contraction • Broncho Constriction

Treatment for action of PGE_1

- Misoprostol (ulcer) Intravenous injection
- Alprostadil (treatment impotence) Intracavernosal injection
- Alprostadil (maintaining – PDA)

Uses of PGE_2

- Enprostil (treatment of ulcer) (gastric secretion decreased)
- Abortion, induction of labor, PPH – dinoprostone is given – uterine contraction
- Bronchial asthma – due to bronchodilation
- Cervical priming – causes cervical ripening

Treatment by PGI_2

- Used to avoid platelet damage – as platelet aggregation is decreased
- Decreases in infarcts size
- Pulmonary hypertension

Treatment by F_2

- Glaucoma
- Induces abortion and treatment of PPH– Dinoprost
- Methyl PGF_2Alpha – Carboprost

PGE_2

- Acts as an **anti-lipolytic agent**
- Mobilizes calcium from bone
- Has got insulin like effect
- Increases anti pituitary hormone
- Has got TSH like effects in thyroid

Dinoprostone

- PGE_2 analogue
- Given by **Intravaginal route**
- Given for cervical ripening

Dinoprost

- PGF_2Alpha analogue
- It induces **mid trimester abortion**
- For controlling PPH

Misoprostol

- PGE_1 analogue
- Used with mifepristone for MTP
- Misoprostol is contraindicated in pregnancy because it causes Mobius syndrome (Abnormal 6 &7 cranial nerve development)

Prostaglandin receptors 00:16:15

DP ↓ Anti-aggregatory action	EP ↓ Enprostil	FP ↓ Fluprostenol	IP ↓ Eicapost Selexipag Used in treatment of pulmonary hyper tension	TP ↓ Seratrodast Treatment of Asthma

- Latanoprost $PGF_{2\alpha}$ - glaucoma

NSAID

Aspirin 00:04:40

- Oldest analgesic
- Most widely used anti-platelet drug
- Irreversible COX inhibitor (Acetylates COX @ serine residue irreversibly)
- Analgesic: weak than morphine
  - HOW → Blockade of PG mediated sensitization of nerve endings
  - FACT → Not effective in sever visceral and ischemic pain
- Anti – Inflammatory and anti-pyretic: @ 100mg/kg/d
  - HOW → Resets hypothalamic thermostat and promotes heat loss
  - FACT → Does not decrease heat production
- Gastric mucosa: Causes mucosal damage
  - HOW → Ion trapping in mucosal cells
  - FACT → Aspiring + CaCo3 + Citric acid → Less ulcerogenic
- Vessels and heart: Vasodilation and increased CO
  - HOW VD → Both TXA2 and PGI2 are inhibited, but, PGI2 is resynthesized
  - HOW increased CO → Na+ & water retention

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- FACT → AT toxic doses → decreased BP → Due to vasomotor center depression

PK

- Undergoes deacetylation in live r
- <2g/d → Urate retention and antagonism of all uricosuric drugs
- 2-5 g/d → Variable effects
- >5 g/d → Urate excretion
- (But >5 g/d is poorly tolerable in patients → So, aspirin is CI in gout)

Fact:

- Acetyl salicyclic acid → Aspirin
- Non – acetylated aspirin → Sodium, magnesium, choline, sodiumthio salicylate, sulfasalazine, mesalamine (5-amino salicylates → Only these can be used for crohn's disease)
- Hypersensitivity → Cross HS seen with other NSAIDS and yellow dye tartrazine → Not seen with magnesium and sodium salicylate
- Also used topically for → Plantar warts, fungal infections and corn → By causing destruction of keratinocytes and dermal epithelia by free acid

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Propionic Acid Derivatives: 00:21:54

Mech:

- Analgesic, Anti-inflammatory, Antipyretic, Ketoprofen → Lysosomal stabilizing action, Naproxen → Most potent, efficacy, better tolerated, Ibuprofen → safest

- PK: Crosses BBB and placenta, Naproxen (Longer acting)
- ADR: Most common → Nausea, Vomiting, GI. Also tinnitus, blurring of vision
- USES: Dysmenorrhoea, RA/OA, Acute gout (Naproxen), Flurbiprofen (Ocular anti-inflammatory)

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Properties	Phenylbutazone	Indomethacin
MECH	- Anti inflammatory - Prodrug → Oxyphenbutazone - Na⁺/water retention → Edema	- Suppress neutrophil motility - At high doses, uncouples oxidative phosphorylation - Inhibits PLA2
PK	- P.O - Completely absorbed - T½ → 60 hrs	- T½ → 2-5 hrs
ADR	- Agranulocytosis - Log term use → Hypothyrodism - SJS - Edema - Ulcer	• Most common → Frontal headache - GI Bleeding - Hypersensitivity - Aplastic anemia - Renal damage
Uses	Only patients who are irresponsive to other NSAIDS	- Closure of PDA (70% success) - Barterr's Syndrome - Acute gout - Ankylosing spondylitis

Properties	Diclofenac	Mephenamic acid
MECH	- Similar to naproxen	- Central and peripheral analgesia - Also a PG receptor antagonist
PK	- Extended therapeutic action of joints	- Slow but complete absorption
ADR	• MC → GI - CNS (Dizziness, nausea) - Skin rashes	• Most common Diarrhoea - Rare → Hemolytic anemia
Uses	- **Similar to brufen** - Post operative and post traumatic pain	- Dysmenorrhoea - Enphenamic acid → No edema

Properties	Piroxicam	Ketorolac
MECH	- Inhibits platelet aggregation - Decreases PG concentration in synovial fluid - Decreases IgM RF	- Potent analgesic - Similar to morphine - Decreases platelet aggregation
PK	- Enterohepatic cycling - Long acting	- P.O/I.M - Glucuronidation
ADR	- Edema - Reversible azotemia - Less ulcerogenic	- GIT, CNS - Skin - Edema - Hepatoxicity
Uses	- Short term analgesic - Long term anti-inflammatory	- Post operative acute musculoskeletal pain - Acute pain

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COX II Inhibitors

Celecoxib:

- Also called as "Safe aspirin"
- Inhibits only COX-2 (No COX-1) (Time dependant and reversible, No Platelet inhibition.
- Cox 2 involved in Ca. colon and Alzheimer's

- ADR: Most common: Abd pain, Diarrhoea, dyspepsia
- Also: Renal toxicity, rarely ulcer (At high doses)
- Inhibits CYP2D6

Facts:

- Lumira coxib and etoricoxib → longest acting, most selective fastest absorption (Lumira > Etori)
- Lumira → Most acidic, Derivative of diclo, banned (Heaptotoxicity)
- Celecoxib → Least selective and most lipid soluble
- Valdecoxib → Shortest acting
- Celec, Valde and pare → Sulfa drugs

Paracetamol 00:32:21

- Diethylated active metabolite of phenacetin, "substitute aspirin"
- MECH:
  - Increase pain threshold, weak anti inflammatory in periphery (weak COX inhibition). Potent COX inhibitor in brain.
- PK:
  - Glucuronidation followed by sulfation. When these get exhausted, glutathione conjugation becomes imp. T ½ → 2-3 hrs.
- ADR:

i. Analgesic nephropathy → Papillary necrosis, tubular atrophy, Renal fibrosis, kidney shrinkage and loss of urine concentrating capacity.

ii. Delayed hepatic necrosis s→ due to glutathione depletion.

DMARD (DISEASE MODIFYING ANTI RHEUMATOID DRUGS) PART - I

Rheumatoid arthritis 00:00:05

- Inflammation of joints
- It is similar to gout
- Characteristic features are – symmetric, persistent, inflammatory, synovitis involving peripheral joints.

Pathophysiology

- IgM immune complexes which develop that activates complements which further activates cytokines release and these is release of lysosomal enzyme.

Treatment 00:02:00

- In acute rheumatoid arthritis NSAID (it inhibits prostaglandin responsible for both pain and vasodilatation)
- DMARD'S are used.

Disease modifying anti-rheumatoid drugs 00:02:47

Methotrexate

- This is a first choice drug
- Dose – 7.5 mg/week

- It inhibits **amino imidazole carboxy amide ribonucleotide** (AICAR)
- There is ongoing accumulation of AICAR due to which there is increased release of adenosine
- This adenosine is going to act as an anti-inflammatory agent
- Adverse reaction – causes **mucositis & hepatotoxicity** (Treatment of mucositis is palifermin)

Sulfasalazine 00:04:50

- Sulfasalazine gets metabolised and concerted to sulfapyridine and 5- amino Salicylic acid.
- Sulfapyridine is used in treatment of Rheumatoid arthritis.
- 5 amino salicylic acids are used in treatment of ulcerative colitis.
- Both these drugs in used only when methotrexate is contraindicated.
- It also causes reversible infertility in male.

Chloroquine & hydroxychloroquine 00:06:06

- Chloroquine might cause – corneal toxicity (**Bull's eye retinopathy**) and corneal opacity, these are less seen by usage of hydroxychloroquine.

Leflunomide 00:06:50

- It is a pro drug.

- It is an isoxaxole Immunomodulatory agent.
- This agent inhibits tyrosine kinase also inhibits **dihydro oratate dehydrogenase** (DHODH)
- Due to inhibition of tyrosine kinase and DHODH it leads to **inhibition of pyrimidine synthesis in dividing cells.**
- Dose – 100mg OD* 3days → 20mg OD (it is a longer acting drug only single dose is given)

Adverse reaction

- Alopecia
- Hypokalaemia
- Weight loss

DMARD [DISEASE MODIFYING ANTI-RHEUMATOID DRUGS] PART-II

Etanercept 00:00:16

- Given via s.c route/week
- TNF- alpha receptor p75 monomer
- Methotrexate is administered in combination with Etanercept.

Monoclonal antibodies 00:02:04

1. Adalimumab (s.c)
2. Infliximab (I.V)
3. Golimumab (s.c)

Adverse reaction includes development of TB, SLE &Lymphoma

4. Certolizumab (pegylated antibody)

Monoclonal Antibodies-Salient features 00:03:55

Drug	Salient features
Anakinra	- IL-I-R competitive antagonist - Short half-life (s.c daily)
Abetacept	- Co stimulation inhibitor - Competes with CD28 for CD80/86 binding
Rituximab	- Anti-CD 20 antibody - For refractory cases

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Tocilizumab	- IL-6-R antagonist - Juvenile idiopathic arthritis
Natalizumab	- Anti-alpha-4 integrin antibody. - IV every month - **Causes progressive multifocal leukoencephalopathy**
Tofacitinib	- JAK-3 inhibitor - Only in MTX resistant cases
Infliximab	- Chimeric IgGK monoclonal antibody - Anti- infliximab antibody reaction - Used for Crohn's disease

Biologicals-salient features 00:07:38

Drug	Adverse effects
Gold	- Diarrhea - Taste disturbances - Alopecia - Dermatitis
Leflunomide	- Diarrhea - Hypokalemia - Weight loss - Alopecia - Increased incidence of respiratory infections - Raised liver enzymes

Natalizumab	- Progressive multifocal leukoencephalopathy
Methotrexate	- Bone marrow depression - Mucositis - Hepatotoxicity - Increased incidence of respiratory infections
Sulfasalazine	- Neutropenia - Thrombocytopenia - Hepatitis - Reversible infertility in male
Chloroquine	- Bull's eye retinopathy - (Less with hydroxychloroquine) - Rash - Greying of hair

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APPLIED PHARMACOLOGY

- Symptoms occur due to increased uric acid concentration in blood
- Asymptomatic hyperuricemia does not need treatment
- Normally uric acid is excreted by organic acid transporters into urine

  It is a slow mechanism, excretion is very slow

  ↓

  Any condition leading to increase in levels of uric acid

  Finally leads to deposition of uric acid in body (Especially in end arteries)

  ↓

  Leading to inflammation & pain

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Gout 00:03:40

Increased synthesis of uric acid

1. Leukemia
2. Lymphoma
3. Rapid weight loss

- cell death is present

Decreased excretion of uric acid

1. Lead nephropathy
2. Glycogen storage disorder

Drugs

Mnemonic "pen and cycle increase urine"

P: Pyrazinamide

E: Ethambutol

N: Nicotinic acid

And: Alcohol / aspirin

Cycle: cyclosporine/cytotoxic drugs

increases urine: Diuretics

→ Hyperuricemia

Treatment 00:07:00

Acute gout

AIM:
- Treatment of pain is important than the treatment of levels of uric acid
  Treatment:
  anti-inflammatory drugs
  NSAIDS preferred.
  eg: - Indomethacin
  Naproxen
  Diclofenac
  Piroxicam
- Previously colchicine used now not used
- If not responding to NSAIDS, steroidal anti-inflammatory drugs are used
  [Intra articular Triamcinolone]
- PCM: It is poor anti-inflammatory

therefore, not used

Chronic Gout

AIM: Decrease the uric acid levels

Decreased synthesis of uric acid

Xanthine oxidase inhibitors

↓

1. Allopurinol
2. Oxypurinol
   (Active metabolite of allopurinol)
3. Febuxostat

Increased excretion of uric acid

Uric acid transporter inhibitors

Prevent absorption of uric acid

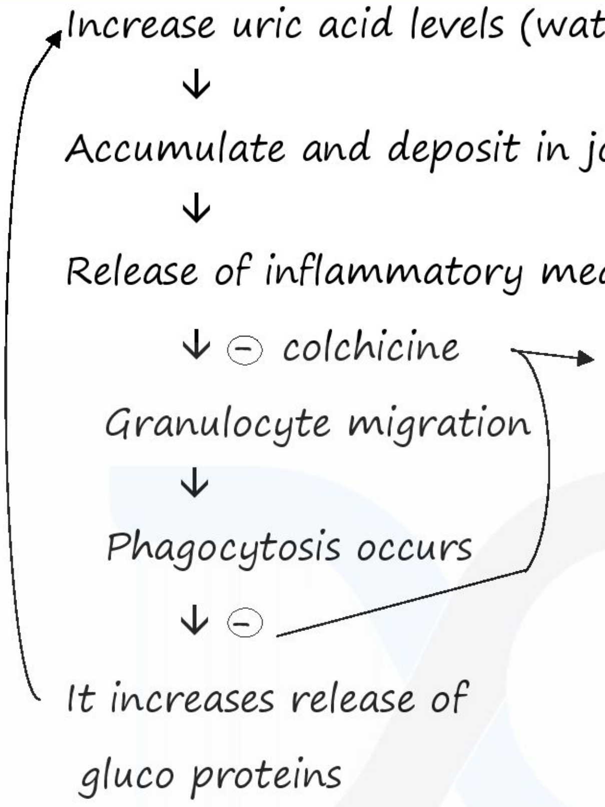
↓

1. Probenecid
2. Sulfinpyrazone
3. Benzbromarone
4. Lesinurad
5. Losartan
6. Fenofibrate

Uricase analogues

1. Rasburicase
2. Pegloticase

Acute Gout 00:15:40



Increase uric acid levels (water insoluble)

↓

Accumulate and deposit in joints

↓

Release of inflammatory mediators

↓ ⊖ colchicine

Granulocyte migration

↓

Phagocytosis occurs

↓ ⊖

It increases release of gluco proteins

Not used

1.via peroral route it cause diarrhea. therefore, NSAID's used

2.IV route: Extravasation and sloughing of skin

Used in

1.Mediterranean fever

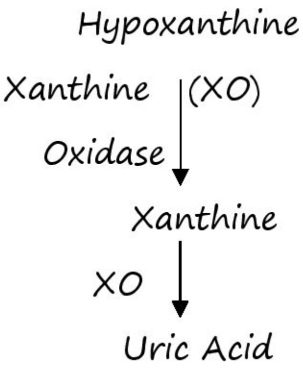
2.Amyloidosis

Chronic gout 00:20:50

Chronic gout

Decreased synthesis: -

1.Allopurinol:



Low Dose of XO: Competitive and reversible inhibitor of xanthine oxidase.

High Dose: Noncompetitive irreversible inhibitor of xanthine oxidase.

Advantage:

1. Decreases size of already established tophi
2. Decreases both serum and urine uric acid levels
3. Inhibit reperfusion injury
4. Can be used in renal failure and renal stones
5. Inhibit de novo purine synthesis
6. Can be used in lesch – Nyhann syndrome

(HGPRT Deficiency: - Triad of: mental retardation
Self-mutilation
Hyperuricemia)

Adverse effects

1. Most common GIT side effects: Nausea, vomiting
2. Dermatitis (Allopurinol hypersensitivity syndrome)
   → rare
   ↓
   - i. Hepatitis
   - ii. Desquamating erythematous rash
   - iii. Worsening renal function
3. Orotic aciduria: Due to inhibition of orotidylate decarboxylase

Other uses

1. Gout nephropathy
2. Urate stones
3. Kala azar (Not used now)

Note:

- Dose must be reduced when given with mercaptopurine and azathioprine
  Therefore, there is increased chances of bone marrow depression
- Dose reduction not necessary with thioguanine
- No interaction with salicylates
- Allopurinol → oxypurinol (Active metabolite)

Uricosuric agents 00:29:10

Probenecid:

- No use in acute attacks
- Only helpful in chronic attacks
- Prevent secretions of
  M: Methotrexate
  A: Acyclovir (HIV)
  C: Cyclosporine (Immuno modulator)
  P: Penicillin – Antibiotics
  C: Cephalosporins / cidofovir
  ↓ ↓
  Antibiotic CMV

Other features

- Rifampicin
- Pyrazinamide
  Ethambutol

They Decrease Biliary excretion of probenecid

- Among all uricosuric agents- probenecid and sulfinpyrazone have rapid per oral absorption
- Salicylates: They decrease actions of probenecid and sulfinpyrazone

Adverse effects:

- GI side effects most common
- Rash
- Renal calculi

  These drugs contraindicated in renal failure.

  Allopurinol → Initially should be given along with NSAID/Colchicine to prevent flare up attacks.

Sulfinpyrazone:

- It is structurally similar to phenylbutazone (NSAID)
- It does not have anti inflammatory

  Analgesic

  Sodium retention property
- It is very long-acting agent
- **Contraindications:**

  1.Gastric ulcer (it increases secretion of gastric acid)

  2.Renal calculi (Hydration can prevent development of renal calculi)

Benzbromarone

- High potent uricosuric agent
- Uricosuric of choice in renal failure
- Can be combined with allopurinol

Contraindications of uricosuric agents: -

1. Urine flow <1ml/min
2. Pre-existing renal calculi
3. Creatinine clearance <50ml/min

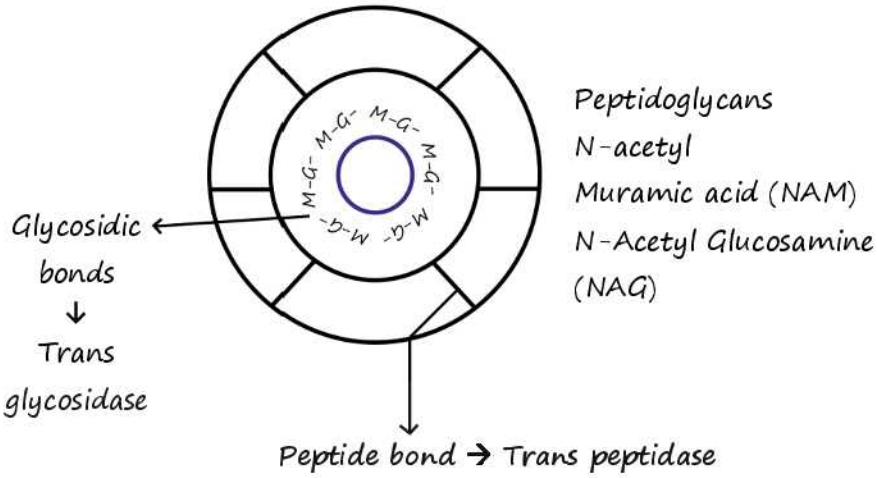
Any 1 is also enough

Uricase analogues 00:40:15

- These tend to produce severe hypersensitivity reaction (But rare)
- In G6PD deficient individuals it can produce hemolytic anemia

  [Rasburicase and Allopurinol can be used in chemotherapy induced hyperuricemia]

CELL WALL SYNTHESIS INHIBITORS


M-G- M-G- M-G- M-G- M-G- M-G-
Peptidoglycans
N-acetyl
Muramic acid (NAM)
N-Acetyl Glucosamine
(NAG)
Glycosidic bonds
↓
Trans glycosidase
Peptide bond → Trans peptidase

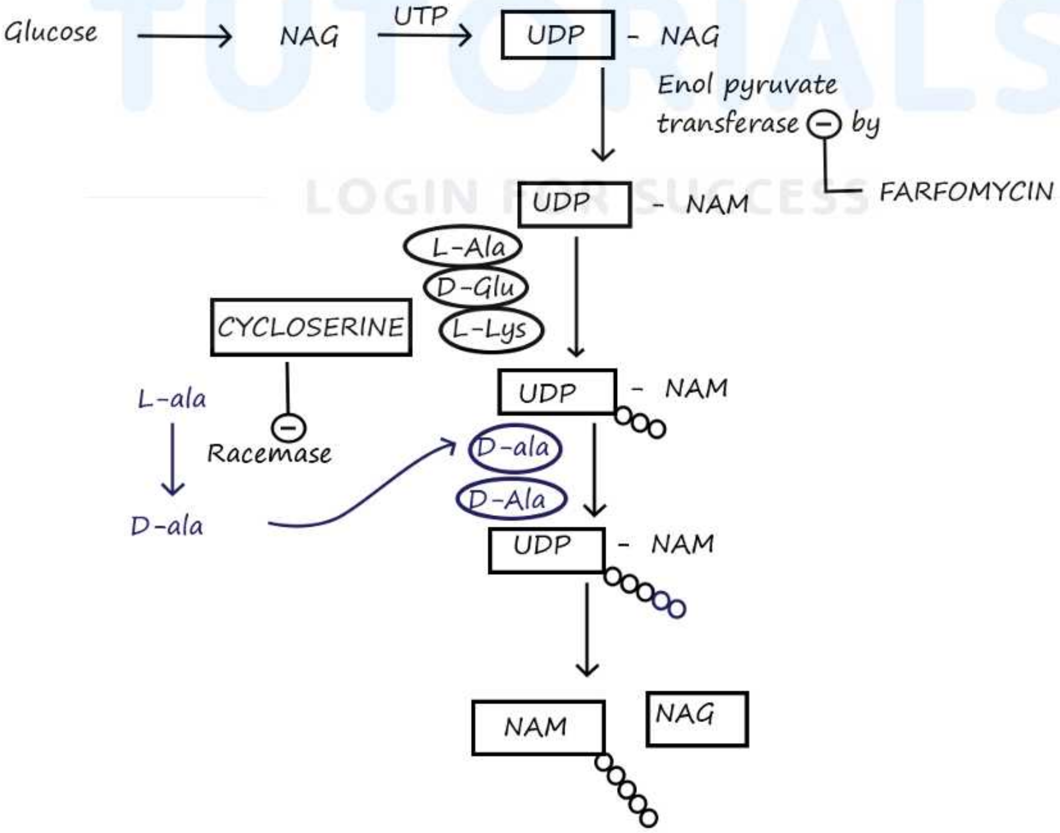
50-100 layers → G positive

1-2 layers → G negative

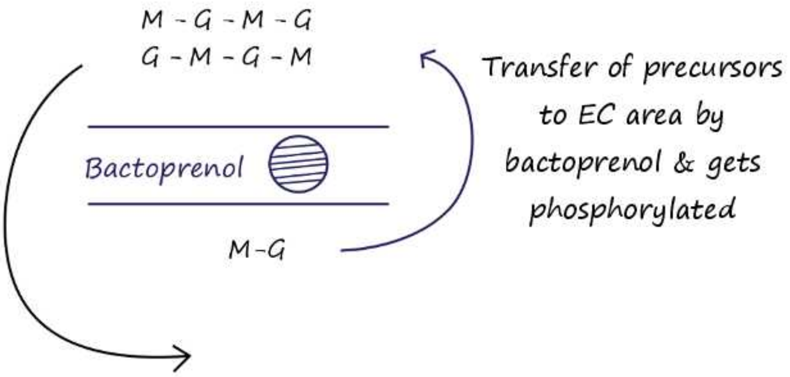
(Additional LPS layer)

Cytoplasmic stage

Synthesis of precursors


Glucose
NAG
UTP
UDP - NAG
Enol pyruvate transferase ⊖ by
FARFOMYCIN
UDP - NAM
L-Ala
D-Glu
L-Lys
CYCLOSERINE
⊖
Racemase
L-ala
D-ala
UDP - NAM
D-ala
D-Ala
UDP - NAM
NAM
NAG

Membrane stage


M - G - M - G
G - M - G - M
Bactoprenol
M-G
Transfer of precursors to EC area by bactoprenol & gets phosphorylated

- Bactoprenol restored after dephosphorylation by phosphatase
- ⊖ → Bacitracin

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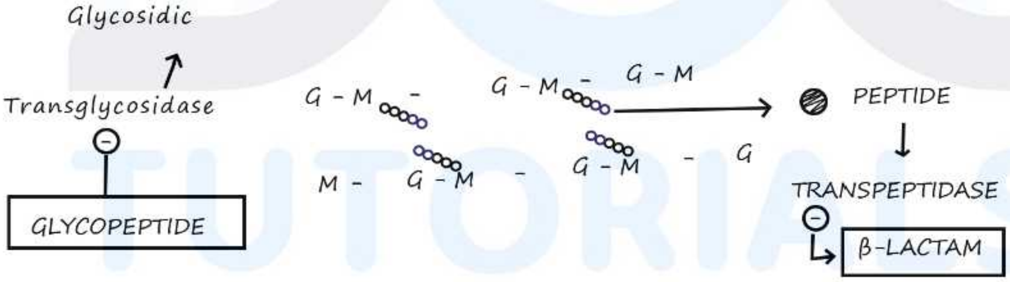
Extracellular


Glycosidic
Transglycosidase
⊖
GLYCOPEPTIDE
G - M
M -
G - M
G - M
G - M
G - M
G
PEPTIDE
TRANSPEPTIDASE
⊖
β-LACTAM

Drugs

- Non-competitive/ irreversible
  1. β-Lactam → ⊖ Transpeptidase
  2. Fosfomycin → ⊖ ENPT
  3. Bacetracin → ⊖ Phosphatase
  4. Glycopeptide → ⊖ Trans Glycosidase and ⊖ D-ala/D-ab
  5. Cycloserine → ⊖ Racemase

Glycopeptide

Natural
↓
CIDAL ← VANCO
But, static teicoplanin for enterococci
↓
Dap to mycin acts as cidal for enterococci

Semi-synthetic
↓
Telavancin
Oritavancin
Balbavancin

Large molecule
&
Ionized

→ G positive

(Reversible)
→ Nephrotoxicity/ ototoxicity

↓
"Red person syndrome"
↓
Histamine & cytokines
Slow IV infusion

Preferred parental
Per oral – Pseudo membranous Enterocolitis (C difficile)

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Uses

- DOC
  - MRSA/ Coagulase negative staph
  - Corynebacterium jejunum
  - Penicillin allergies patients

- Clostridium difficile

Resistance

VISA
i. Thickened cell wall
ii. Dala decoys

VRSA
i. Dala & β-lactate

Teicoplanin

- TDM for seriously ill & renal failure
- Lipophile
- Long DOA
- Less Redman/ Nephro

Semisynthetic

1. Telavancin → Disrupts membrane potential CSSS1
2. Palbavancin
   - O/W
   - VRSA
3. Oritavarcin

β-Lactam

Penicillin's

1. 6-amino penicillanic acid
2. Cidal (activity multiplying) TDK
3. Transpeptidase inhibits (pencillin buiding proteins)

↓

Osmotic rupture

Cephalosporins

1. 7-amino cephalon sporamic acid
2. Cidal TDK
3. Transpeptidase inhibitor

- β-Lactamase
- Mycoplasma
- IV generation → Resistance against β-lactam
- Except – metaelo β-lactamase
- KPC
- Classification – I, II, III, IV

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- Cefamycin – contains 7-α methoxy group

↓

Resis to ESBS

- Example: Cefoxitin, cefotetan, cefentazole

4. Resistance

β-Lactamase

a. Hydrolyser, β-lactam ring

b. ⊖ - Bactam

- Mycoplasma - Classification

- NSPSA
- VNSPRA
- WSPSA

Narrow spectrum

1. Penicillin G (Im/IV)
   - Benzathine (I.m.)
   - Procaine (I.m)
   - Phenoxy methyl
2. Anti – staph
   - Flucloxacillin
   - Methicillin
   - Oxacillin
3. Broad spectrum
   - Amox
   - Ampi
   - Co-amox – clav
   - Piv mecillemaan (P.O. ESBL, UTI)
   - Temocillin → X-metallo β-lactam
   - All P.O penicillium → Empty stomach (Food delays absorption)

4. Anti – pseudomonal
   - Doc – AG + ureido – P
   - Not mixed in same fluid
   - Ureido – P inactivates AC
     a. Carboxy (Carbenicillin ticarcillin) P.E
     b. Ureido (Mezlo, Azlo, pipes)
   - Safest penicillin in renal failure
   - First order kinetics to order (as dose ↑↑)

Cef

- 1st generation except cefradine
- Pine
- Pirome
- (-val) → 5th

- 3rd tid P.O
- t → Ceftibuten, tniauone, Tizoxine, Tizidimo
- i → Cefinime
- d → Cefditoren
- P → Cefpodonime
- O → Cyloperazone otanime

2nd Proton

Cefprozil

Cefotetan

Cefoxitin (B. fragilin)

Mu → Cefuroxime

Cefamandole

- Horacarbef → 2nd
- Monolactam → 3rd
- Ceftolozane – Tazobactam
- All 3rd generation → Good CNS except cefoperazone

- Marker for ESBL detection

1. Cef podonime
2. Cef tazidime
3. Cefo trauma
4. Ceftriaxone
5. Aztreonam

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- Cefolozane – Tazobactam

  1. All 3rd gen → good CNS

     Except → Cefoperazone

     Furine

     Furoxime

  2. Urine (many excreted unchanged) → except

     cefotaxime → disacetyl metabolites

     Except – ceforianone (long t 1/2)

     Cefoperazone

  3. Protein acid increases t ½ (Dose reduction in renal failure)

ADR

Least – PO

Most – topical

i. Hypersensitivity reactions

Rarely fatal (1:1,00,000)

- 19E media red reaction
- Causes urticaria
- Intradermal skin testing

  Benzyl penicillyl polylysine

  Cross allergy – a. Partial – β – factor & cephalosporin

  b. Low: penicillins & carbapenem

  c. 0% – Penicillins & monobactarm

ii. GIT – Diarrhea P.O preparation

Ampicillin > Amoxicillin

Specific ADRS

1. Methi → Interstitial nephritis
2. Naf - Neutropenia (reversible)
3. Amp – PME (most common cause)
4. Oxacillin – Hepatitis
5. Carbenicillin – bleeding
6. Flucloxacillin – Cholestasis jaundice

- High dose β lactam x 10 days

↓

Neutropenia

Convulsion

Hepato toxicity

Cephalosporins ADRS

i. Hypersensitivity most common – maculo popular rash bone marrow depression

ii. Pain at site of injection

iii. Reversible thrombocytopenia, Hemolytic anemia, Neutropenia, Interstitial nephritis

iv. 3rd → Opportunistic (Candida/c. difficulo)

Specific ADRS

- Cytrianone – biliary sludging
  - Cholelithiasis
  - → Palpitation
- Do not give calcium containing products.

↓

Calcium salt

↓

Biliary pseudo – Lithiasis

- Drug with methyl thio tetrazole ring (MTT ring)
  - Cefmandole
  - Ceforperazone
  - Moxarlactram
  - Cefotefan

Disulfiram reactive

Bleeding thrombocytopenia

- Hybrid [Penicillin + Cephalosporin] → Renem

E.g. – Faropenem

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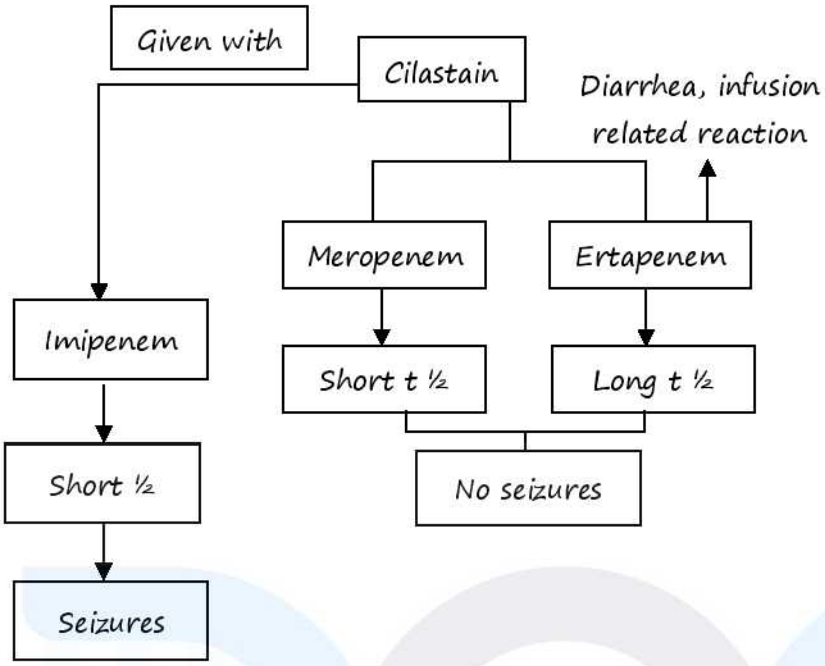
- CARBAPENEM (widest spectrum)


Given with
Cilastain
Diarrhea, infusion related reaction
Imipenem
Meropenem
Ertapenem
Short ½
Short t ½
Long t ½
Seizures
No seizures

– Lumipenem + DHP → Breakdown products

Inactive　　Nephrotoxic

Resistance to carbapenem

	Natural	Acquired
DOC	i. steno	i. Enterobacteriaceae
Cotrima	trophomones	ii.Pseudomonas
zole	mactrphilia	iii. Klebsiella
	ii. Elizabeth	↓ mechanism
	Kingella	i. ESBL with porin loss
	meningo	ii.Carbapenemase
	septuca	(plasmid bone)
	↓ meaning	↓
		Types

i. Chromosomal metallo β – lactamase (α_1 & α_2)

i. Kpc (k. Pneum carbapenemase)

ii. Ndm (new delhi metallo β – lactamase)

iii. Vim (verona integron metalo β lactanase)

iv. Oxa - 4δ (oxacillinase)

Aztreonam [Pseudo/H influenza/N. meningitidis/ N. gonorrhea]

↓ "Heart cross allergy with penicillins"

- Binds to TBP – 111
- IV/IM
- Can be used for KPC
- Not used → Metallo β-lactamase

- Structure – similar to ceftazidime

  (Cross reactions to Ceftazidime)
- Anti MIC spectrum – similar to Aminoglycosides
- ADR – Rash/Hepato toxicity/ Pain at injection site

Colistin 00:04:18

- Itself is Highly toxin
- **Colistin methane sulfonate (less toxic)**
- Colistin is always given in combination to prevent the development of resistance.
- Most commonly combined with Meropenem
- Concentration Dependent Kinetics property
  - Adverse reaction
    i. Reversible hypokalemia
    ii. Bacteria like Syndrome

Daptomycin 00:06:03

- It is a cyclic lipopeptide antibiotics
- It is **drug of choice for VRSA (extra pulmonary)**
- The Daptomycin is broken down by surfactant due to which it is **not a drug of choice for pulmonary diseases due to vancomycin resistant**

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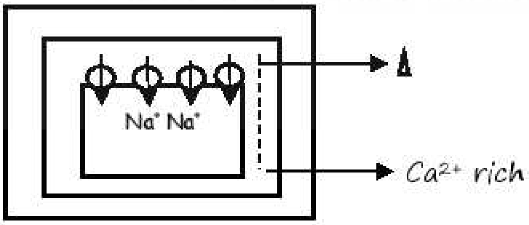

- **Ca^{2+} ions are reach in the cell that causes conformational change in structure of Daptomycin**
- The Daptomycin is incorporated on the cell membrane
- As the Daptomycin area into intracellular area
- This leads to influx of ions (Na^{+}) in the cell

DRUGS AFFECTING BACTERIAL CELL MEMBRANE

PO →

- Polypeptides
- Polymyxin Colistin
- Polyenes
- DA → Distamycin

Polypeptide antibodies 00:00:52

- These are cationic in nature
- The polypeptide binds to anionic outer cell membrane that causes bacterial cell death

- The polypeptide binds to anionic outer cell membrane
- Ionized drugs impenetrable & water soluble
- Polypeptide drugs are impenetrable & water soluble
- These polypeptide drugs are effective against gram negative bacteria
- As it is water soluble, Nephrotoxicity can occur

Adverse Reactions

- Nephrotoxicity
- Neurotoxicity
- NM blockade

- Due incorporated cell membrane it leads to rapid depolarization
- This rapid depolarization causes loss of membrane potential leading to cell death
- Concertation killing is seen by these drugs and excreted by kidney
- As Daptomycin is broken down by a surfactant, it **causes an adverse reaction of eosinophilic pneumonia, myopathy, rhabdomyolysis & hypertension**
  - Therapeutic uses of these drugs are missing or Spectrum of activity
- The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a deter- gent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and cell death.
- Polymyxins are concentration- dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter spp, and Enterobacter spp.
- However, alterations in the cell membrane Lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant.
- Only two forms of polymyxin B are in clinical use today, **polymyxin B** and colistin (**polymyxin** E).

DRUGS AFFECTING BACTERIAL PROTEIN SYNTHESIS – I (AMINOGLYCOSIDES)

Drugs inhibiting protein synthesis 00:00:20

- Aminoglycosides
- Macrolides
- Tetracycline
- Chloramphenicol

Other

- **Mnemonic: Protein loss FM**
  - P – pleuromutilin
    - Pleuromycin
  - Lincosamides
  - O → Oxazolidinones
  - S → Streptogramins
  - S → sordarin
    - Spectinomycin
  - F → Fusidic acid
  - M → mupirocin

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Aminoglycosides 00:01:56

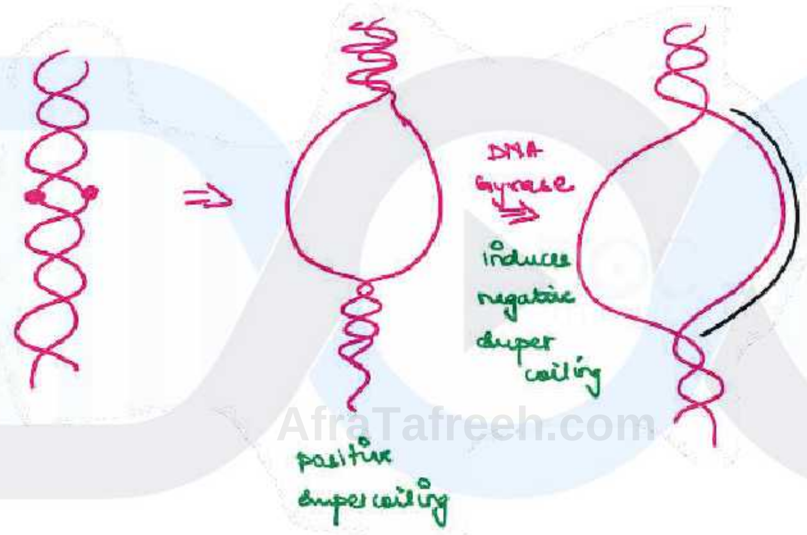
- These are amino sugar joined by glycosidic linkages.
- These are derived from soil actinomycetes.

Soil actinomycetes

Streptomyces → - mycin

Micromonospora → - micin

Mechanism of Action:



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Gram negative organism

- Gram negative organism has got outer coat then cell wall, which contain ribosomes.
- Aminoglycoside crosses the outer wall and reaches the periplasmic space. Amino glycoside cannot cross this membrane.
- The cell wall contains O_2 dependent phase 2 entry through which the amino glycoside passes and reaches the cytoplasm, thus binds to the Ribosomes binds with 30s and cause MIT - misreading of

codon, initiation of protein synthesis, termination of Protein Synthesis.

- Mnemonic: Pick OATS TDS
  - O – oxazolid
  - A – Amino glycosides
  - T – Tetracycline
  - S – Spectinomycin

Aminoglycosides – Pharmacokinetics 00:08:30

- Ionized drugs – impenetrable and water soluble
- Not given by a peroral route except

i. Neomycin

↓

Can be used as

- Pre-of pre-operative gut sterilization
- Hepatic coma

ii. Paromomycin

- Can be administered IV/IM
- Not bound to plasma proteins
- Does not cross BBB
- Excreted by Kidneys
- Long post antibiotic effect
- CDK

Adverse reactions 00:12:36

- NO → Ototoxicity
  - ↳ Nephrotoxicity/NM block
- Nephrotoxicity – (Reversible)
- Proximal tubular cells
- Albuminuria
- Loss of urine concentrating capacity.
- It is maximum with drug neomycin and minimum with streptomycin.

Neuromuscular blockade

- It is contraindicated in myasthenia gravis as it causes curare like effects.
- This curare effects are maximum neomycin and minimum with tobramycin.
  - Treatment of N.M blockade
- I.V calcium

Ototoxicity (irreversible)

- Gets concentrated in labyrinthine fluid.
- There will be direct hair cell toxicity.
- Damage of both vestibular & auditory can be seen,
  - Tinnitus → deafness
- Progressive and permanent damage is seen

Tinnitus → Deafness

Vestibule toxicity Guest	Auditory toxicity
- G – gentamycin	- Amikacin (causes max damage)
- St – streptomycin	- Kanamycin
	- Neomycin

- Minimum is with – Netilmicin
- With tobramycin vestibular and Auditory both have equal toxicity.
  - Uses–
    - Used for gram negative aerobes.
    - Synergism with penicillins.
    - Some can be used for tuberculosis.

Wonder drug - Plazomycin 00:20:08

- It is effective against for both gram positive and gram negative.
- Least oto/nephrotoxicity
- Given by IV route
- Resistant to other Aminoglycoside's (including CRE)
- Targets AME's (aminoglycosides modifying enzymes)

DRUGS AFFECTING BACTERIAL PROTEIN SYNTHESIS PART – II (MACROLIDES)

Macrolides - structure 00:00:16

- Bigger in size → large macrocyline lactone ring to which sugar molecules are attached

Drugs 00:00:45

- Have suffix "romycin "
- Erythromycin
- Rorithromycin
- Clarithromycin
- Azithromycin

Mechanism of action 00:01:44

- Binds with 50S part of ribosomes and inhibits translocation of newly synthesized peptide from 'A' to 'P' site.
- 'A' site is where tRNA bring amino acids to get attached to peptide chain which is at 'P' site.

Drug interactions 00:08:30

- Microsomal enzyme inhibitors.
- Least inhibiting activity is seen in Azithromycin.

Adverse Reaction 00:09:00

- Mnemonic – macr 'OLID'
- O → ototoxicity (reversible)
- Li → Liver toxicity (Cholestatic jaundice)
- O → Diarrhea (because of motilin receptor against property)
- When motilin hormone binds to motilin receptor present in stomach and small intestine it induces peristalsis.
- Macrolides are structurally similar to motilin hormone and acts as against.

Macrolide Non antibiotic drugs

i. Camicinal
ii. Metemicinal } Motilin receptor against
iii. Tacrolimus → Immunosuppressant

- Fidaxomicin is a poorly absorbable macrolide.

Uses

- Mnemonic – 'mac PL'
- M → Mycoplasma
- A → Alternate to penicillin
- C → Chlamydia/ Corynebacter / Chancroid/ Campylobacter
- P → Pertussis
- L → Legionella

Pharmaco kinetic features

i. Erythromycin → Excreted in bile

ii. Azithromycin → Longest acting because of high volume of Distribution. It can be given Once Daily

- Erythromycin estolate has highest hepatotoxic property

Wonder drug-Ketolide

- Telithromycin → more hepatotoxicity
- Solithromycin → 20x stronger Ribosomal binding
- Cethromycin → inhibits CYP3A4

- Spectrum of activity?

- Erythromycin is highly active against Str. pyogenes and Str. pneumoniae, N. gonorrhoeae, Clostridia, C. diphtheriae and Listeria, but penicillin-resistant Staphylococci and Streptococci are now resistant to erythromycin also.
- In addition, Campylobacter, Legionella, Branhamella catarrhalis, Gardnerella vagina lis and Mycoplasma, that are not affected by penicillin, are highly sensitive to erythromycin. Few others, including H. ducreyi, H. influenza, B. pertussis, Chlamydia trachomatis, Str. viridans, N. meningitidis and Rickettsiae are moderately sensitive. Enterobacteriaceae, other gram-negative bacilli and B. fragilis are not inhibited.

- Clarithromycin: Clarithromycin has activity similar to erythromycin, but it is also effective against Haemophilus influenzae and has greater activity against intracellular pathogens such as Chlamydia, Legionella, Moraxella, Ureaplasma species, and Helicobacter pylori.
- Roxithromycin: Roxithromycin is a long-acting acid stable semi synthetic derivative of erythromycin with an N-oxime side chain on the lactone ring having antibacterial and antimalarial activities. Roxithromycin gets highly concentrated in polymorphonuclear leukocytes and macrophages and exhibits intracellular bacte- virucidal activity. It is also reported to enhance the adhesive and chemotactic functions of cells which in the presence of infection produce phagocytosis and bacterial lysis. It shows potent activity against Gardnerella vaginalis, Moraxella catarrhalis (Branhamella catarrhalis), Haemophilus ducreyi, etc.)
- Azithromycin: Although less active than erythromycin against streptococci and staphylococci, azithromycin is far more active against respiratory pathogens such as H. influenzae and Moraxella catarrhalis. Extensive use of azithromycin has resulted in growing Streptococcus pneumoniae resistance.

DRUGS AFFECTING BACTERIAL PROTEIN SYNTHESIS – III (TETRACYCLINES AND CHLORAMPHENICOL)

Tetracyclines 00:00:15

Tetracyclines

Short acting (~ 6hrs)
↓
Chlortetracycline.
Oxytetracycline.
Tetracycline.
↓
Natural derivatives
↓
p.o route

Intermediate acting (~12hrs)
↓
Methacycline
Demeclocycline.
↓
Semi synthetic.
↓
p.o route

Long acting (~18-24hrs)
↓
Minocycline-most potent
Doxycycline.
↓
Semisynthetic
↓
Iv route

Pharmacokinetics 00:02:42

i. Food affects the absorption of all tetra cyclines except minocycline & doxycycline (IV route)

ii. All are excreted via kidney except long-acting tetra cyclines

iii. Minocycline & doxycycline undergo enterohepatic circulation, hence, have a long t1/2

iv. IM tetracycline injections are contraindicated as they are extremely painful

v. Cross placenta

Adverse reactions 00:04:14

Mnemonic: KAPILDEVS BAT

1. K → kidney →
   - PCT damage (Fanconi's syndrome) except doxycycline.
   - Fanconi's syndrome is also seen if one injects outdated tetracycline.
2. A → antianabolic effects →Due to increased levels of nitrogen.
3. P → phototoxicity → demeclocycline causes dermatdogical side effects.
4. I → intracranial pressure increases → Pseudo tumor cerebri.
5. L → liver damage → @ high doses only.
6. D → diarrhea & DI (nephrogenic).
   - Diarrhea prevented when tetracyclines are given along with food
   - DI → demeclocycline
7. E → enhanced sensitivity (hypersensitivity).
8. V → vestibular toxicity (maximum with minocycline).
9. S → super infection.
10. B → bone.
11. A →And.

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12. T → teeth deformities teratogenic (tetracycline chelates Ca+ and forms calcium orthophosphate complex.

Tetracyclines

- **At high doses** ↓ Hepatotoxicity
- **For longer duration** ↓ Bone & teeth deformities
- **At high doses for longer duration** ↓ Anti-anabolic effects

Tigecycline 00:10:28

- A derivative of minocycline
- Used in MRSA + VRSA
- Not effective against pseudomonas & proteins
- Safe in RF
- Used only in case of severe life-threatening conditions.
- Omadacycline → used in community acquired bacterial pneumonia (CABP)
- Eravacycline → used in complicated abdominal infections

Chloramphenicol 00:12:02

- First completely synthetic drug (1947)
- MOA → Binds to 50 s ribosomal subunit & inhibits "p" site
- Chloral phenol has excellent tissue penetration (CSF penetration is maximum) amongst all antibiotics

Adverse drug reaction

i. GI symptoms

ii. Bone narrow suppression (Dose dependent aplastic anemia reversible but fatal)

iii. Grey baby syndrome (less glucuronidation reactions occur in children & hence chloramphenicol accumulates in them)

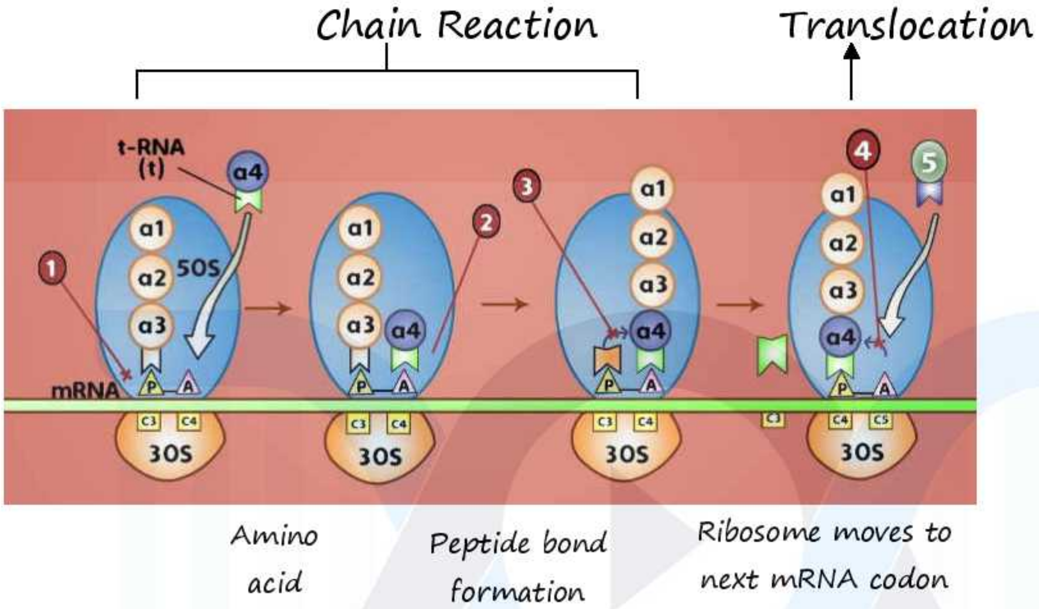
- Vomiting
- Refusal of feeds
- Hypotonic
- Hypothermia
- Ashen grey cyanosis

iv. Superinfection is also seen

- Spectrum of activity of tetracycline's

Antimicrobial spectrum

- When originally introduced, tetracycline's inhibited practically all types of pathogenic microorganisms except fungi and viruses; hence the name 'broadspectrum antibiotic'. However, promiscuous and often indiscriminate use has gradually narrowed the field of their usefulness


Chain Reaction
Translocation
t-RNA (t)
a4
a1
a2
a3
50S
mRNA
P
A
c3
c4
c5
30S
1
2
3
4
5
Amino acid
Peptide bond formation
Ribosome moves to next mRNA codon

- The messenger RNA (MRNA) attaches to the 30S ribosome. The initiation complex of MRNA starts protein synthesis only some formation. The nascent peptide chain is attached to the peptidyl (P) site of the 50S ribosome. The next ino acid (a) is transported to the acceptor (A) site of the ribosome by its specific IRNA which is complementary ae base sequence of the next MRNA codon (C). The nascent peptide chain is transferred to the newly attached acid by peptide bond formation. The elongated peptide chain is shifted back from the 'A' to the "P' site and the ribosome moves along the mRNA to expose the next codon for amino acid attachment. Finally, the process is terminated by the termination complex and the protein is released.

- 1. Aminoglycosides bind to several sites at 30S and 50S subunits as well as to their interface-freeze initiation, interfere with polysome formation and cause misreading of MRNA code.
- 2. Tetracyclines bind to 30 ribosomes and inhibit aminoacyl tANA attachment to the 'A' site.
- 3. Chloramphenicol binds to 50S subunit-interferes with peptide bond formation and transfer of peptide chain from 'P' site.
- 4. Erythromycin and clindamycin also bind to 50S ribosome and hinder translocation of the elongated peptide chain back from 'A' site to 'P' site and the ribosome does not move along the mRNA to expose the next codon. Peptide synthesis may be prematurely terminated.

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DRUGS AFFECTING BACTERIAL PROTEIN SYNTHESIS PART – IV (MISCELLANEOUS)

- Drugs affecting the Nucleic Acid synthesis (NAS)
  - Quinolones
  - Fluoroquinolones
  - Nitrofurantoin
  - Novobiocin
  - Actinomycin D
  - Metronidazole
  - Rifampicin & clofazimine

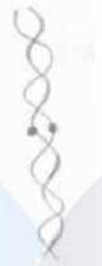
Fluoroquinolones: 00:01:00

i. Mechanism of action –Inhibits DNA gyrase and topoisomerase 4 in susceptible bacteria

- Entirely based on how parent cell DNA is to be copied out to the daughter DNA.
- Parent DNA is circular in nature.
- In order to replicate the individual part of DNA, the two DNA segments must be separated out in order to produce the complimentary of DNA or to produce the daughter segments.
- Whenever this circular DNA is interlinked when it holds of two different segments there is going to be

positive supercoiling in the upper part and lower part.

- In order to remove it we have to start proliferating the individual nuclei acid DNA by separating two strands we can two separate strands of DNA & can start copying it.



- If it is a linear segment if we just pull it out the opposite strands will start moving in opposite direction so no positive supercoil or no tension in that.
- We have separated central part of the nuclei strand but on the upper 7 lower ends supercoiling can be seen.

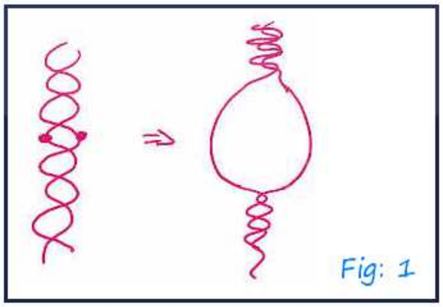


Fig: 1

- As it a circular DNA, particular enzyme is needed in order to produce negative supercoiling this property is called as positive supercoiling, it is a natural phenomenon occurs whenever there is replication process.

- DNA gyrase, will induce negative supercoiling so the tension is going to be relieved out in the nuclear acid.

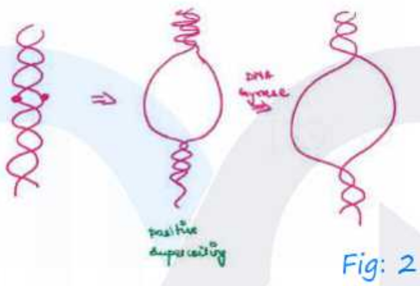


Fig: 2

- Separated form of DNA replication process starts to occur.
- This DNA gyrase enzyme is going to be inhibited when it is inhibited there is no induction of supercoiling more positive supercoiling leads to further damage of the DNA.
- There is circular parent DNA attached to the daughter DNA.
- The parent DNA must be separated from the daughter DNA, as they are interlinked.
- Individual nuclei acid has to be broken down & fused back together.

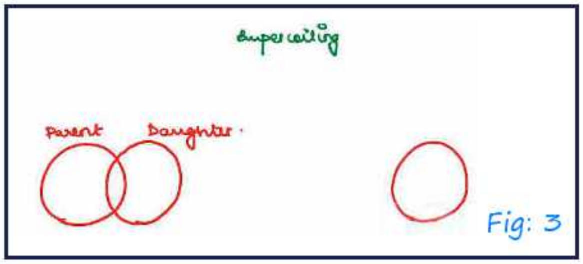

Supercoiling
Parent
Daughter

Fig: 3

- This break and resealing are done by an enzyme called topoisomerase 4 it is also inhibited by fluoroquinolones.

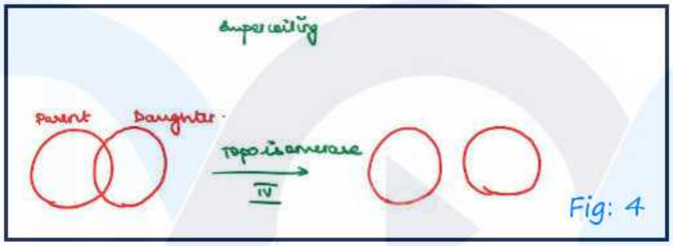

Supercoiling
Parent
Daughter
Topoisomerase
IV

Fig: 4

- Fluoroquinolones inhibits separation, if it is not separated at one point of time cells break down.

Fluoroquinolones

⊖ DNA gyrase
↓
Interferes with correction of supercoiling
↓
Damage DNA
↓
Seen in gram negative organisms

⊖ Topoisomerase IV
↓
separation of daughter DNA
↓
Seen in gram negative organisms
↓
seen in gram positive organisms

Bactericidal agents.

Topoisomerase
↑
Mnemonic: $\boxed{\text{To positive}}$ → gram-positive bacteria.

Characteristic features of individual drugs:

00:06:55

- Ciprofloxacin	Least QT prolong effective against pseudomonas
- Norfloxacin (narrow spectrum antibiotic)	Minimum per oral bioavailability
- Levofloxacin	Maximum per oral bioavailability (~100% effective against pseudomonas
- Gatifloxacin - Gemifloxacin Respiratory flour quinolones	Maximum hypoglycemia
- Moxifloxacin - Trovafloxacin wide spectrum	Maximum QT prolongation
	Maximum QT prolongation

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- Sparfloxacin - Peffloxacin	Electrolyzed by liver and excreted
	Out by kidney

- Moxifloxacin and trasafloxacin are wide spectrum (include an Anaerobes).

Drugs which are metabolized by liver:

- Pefloxacin.
- Gemifloxacin.
- Sparfloxacin.
- Moxifloxacin.
- These drugs are contraindicated in liver failure.

Drugs which are metabolized by kidney:

- Lomefloxacin
- Levofloxacin
- Ofloxacin

contraindicated in renal failure.

- Moxifloxacin is the safest drug in renal failure.
- Sparfloxacin causes TDS-torsade's De pointes for which treatment is magnesium sulphate.

Adverse reactions & contra indications:

i. Fluor Quinolones are contraindicated in:
  - Children (causes tendinitis/tendon rupture).

ii. Fluor quinolones are not effective in:

- Anaerobes (Except moxifloxacin
- Bacteroides
- Clostridium

iii. Most common drug reaction is gastro intestinal distress (GI distress).

Drug interactions 00:12:27

- Not given with:
  - Warfarin
  - Theophylline
  - Caffeine

  ] Metabolism is inhibited by quinolones

  - It causes accumulation of those drugs because of which it causes adverse drug reactions.
  - Fluoroquinolones are not given with NSAID it has GABA displacing action from GABA receptors.

    GABA is an inhibitory neurotransmitter.

    ↓

  - Due to which NSAID with flour quinolones acts as an epileptogenic.

Recent adverse drug reaction:

- Peripheral neuropathy.
- 2 two times more risk of aortic aneurysm
- Hypoglycemia specially with hypoglycemic agents.

Nitrofurantoin 00:15:02

- Acts as static drug.
- All the drugs which inhibit nucleic acid are cidal drugs but this is static drug.
- Effective against many gram-negative organisms not effective against pseudomonas and protease)
- This drug when taken in by per oral routes it roams in body but does not get activated gets activated only when gains entry to urine as it gets activated only in Acidic Ph.
- After getting activated kills the gram negative.
- Negative organisms which are present in urinary tract which is predisposing the urinary tract infections.
- Used exclusively for urinary tract infections.
    - In urinary tract infections usually, urinary alkalinizing agent is given with antibiotic.
    - If alkalinizing agent is given with nitrofurantoin, it does not get activated and combination becomes irrational so effective only in acidic urine.

Adverse drug effects:

- Gastrointestinal effects.
- Pulmonary fibrosis
- Hemolysis in G6PD deficiency.

Novobiocin 00:17:13

- Amino Coumadin antibiotic.
- Static drug
- Similar to fluoroquinolones mechanism of action inhibits DNA gyrase especially in staphylococcus epidermis that's why it is used only in cultures not used for treatment purposes.

Nalidixic acid (quinolones):

- Inhibits DNA gyrase.

Adverse effect:

- Glycosuria
- Neurotoxicity
- Photo sensitivity (dermatological reactions can be seen).
- Nitrofurantoin antagonizes the actions of nalidixic acid.
- Spectrum of activity?
  - First-generation compounds (for example, nalidixic acid) were spectrum Um narrow-spectrum agents with activity against aerobic gram-negative bacillus, mostly Enterobacteriaceae. Second-generation compounds (for example, ciprofloxacin) exhibit improved intracellular

penetration and broadened coverage which includes Enterobacteriaceae, Pseudomonas aeruginosa,

- Haemophilus influenzae, Neisseria spp. Chlamydia spp, and Legionella Spp. Third-generation compounds (for example,
- levofloxacin) maintain the bacterial spectrum of sec- and generation agents, with improved activity against Streptococcus spp. including S. pneumoniae, methicillin-susceptible Staphylococcus aureus. Stenotrophomonas maltophilia, and Mycobacterium Spp.
- Fourth-generation compounds (moxifloxacin, gemifloxacin, and delafloxacin) have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp. Delafloxacin has activity against methicillin-resistant Staphylococcus aureus and
- Enterococcus faecalis. Further, delafloxacin and moxifloxacin have activity against Bacteroides fragilis and Prevotella spp, while maintaining activity against Enterobacteriaceae and Haemophilus influenzae. From this group, only delafloxacin has activity against P. aeruginosa. Lastly, these agents maintain atypical coverage,

with moxifloxacin and delafloxacin showing activity against Mycobacteria spp.

DRUGS AFFECTING BACTERIAL NUCLEIC ACID

Pleuromutilin 00:00:10

- Includes
  - Retapamulin
  - Lefamulin
- M.O.A
  - 50S ribosomal inhibition (binds to domain V of 23s RNA)
- Pharmacokinetics
  - Bacteriostatic at therapeutic concentration
  - Bactericidal at higher concentration, 94% PPB
  - Metabolised by CYP3A4
- Use
  - Topical for impetigo due to MSSA/ streptococcus pyogenes

Lincosamides (Clindamycin, Lincomycin) 00:01:48

- M.O.A → similar to macrolides
- Clindamyan effective against anaerobic organisms, good oral absorption, No CSF distribution, skin rash.
- Clindamycin may cause pseudomembranous enter colitis.
- Pirlimycin is an analogue of clindamycin
- Cross resistance seen with macrolides, Lincosamides and Streptogrammins
- Clindamycin is safe in pregnant women & children

Oxazolidinones 00:02:57

- Linezolid
- Binds to 23s part of 50s submit and inhibits INITIATION of protein synthesis
- No activity on gram negative organisms
- No activity on an act on gram positive
- No cross Resistance (due to additional action on 30s, 50s,30-50s)
- Adverse effects
  - Thrombocytopenia
  - Neutropenia
  - Serotonin syndrome
  - Most common: Diarrhoea, Headache
  - Also, optic neuritis, lactic acidosis, peripheral neuropathy
- Oral Bio availability → 100%
- Normal Dose → 10mg/kg daily
- No dose adjustments in Renal Failure
- Drug of choice for VRE, Pulmonary VRSA, XDR-TB (reserve drug)

Streptogrammins 00:05:35

- M.O.A → 50s inhibition, tRNA synthetase inhibition
- Drugs
  - Streptogrammin A – Dalfopristin
  - Streptogrammin B – Quinopristin

  - Monotherapy → Bacteriostatic
  - **70:30 ratio → Bactericidal**
- Adverse effects → venous irritation, arthralgia – myalgia syndrome

Mupirocin 00:06:15

- For staphylococcus nasal carriage elimination (nasal spray)

- **FUSIDIC ACID**
  - Steroid antibiotic
  - Topical for staphylococcus
  - Prevents turnover of elongation factor from ribosome

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DRUGS AFFECTING FOLIC ACID SYNTHESIS

Sulfonamides 00:00:15

- **Short acting** → Drugs ending with "azole" or "zine".
  - Drugs ending with "azole" or "zine".
    - Sulfisoxazole
    - Sulfadiazine

- **Intermediate acting** → Drugs ending with "azole".
  - Sulfamethoxazole.

- **Long acting** → drugs ending with "zine"
  - Sulfamethoxypyridazine
  - Sulfadoxine

- Poorly absorbable → **Sulfasalazine** (colitis) (mesalamine)

- Topical
  - Sulfacetamide
  - Mafenide
  - Silver sulfadiazine

M.O.A

Pteridine → Dihydropteroate Synthetase

PABA → Folic acid synthetase

↓

Dihydropteroic acid

↓

DHFA

↓ DHFR

THFA

↓

Nuclear precursors for NA synthesis

- Sulfonamides inhibit folic acid synthetase and dihydropteroate synthetase as they are PABA analogues.
- Trimethoprim inhibits DHFR enzymes.
- Sequential blockade = Sulfonamides + trimethoprim
- We combine trimethoprim with only sulfamethoxazole as they share same duration of action & hence reach peak at the same time.

- "2 BHK with maruti car parking" ("t" capital)
  - 2B → PABA analogue (MOA
  - 2H → Hypersensitivity — Hemolytic anemia

    Adverse drug effects
  - 2K → kidney (hematuria, crystalluria)

    Kernicterus

- M → Malaria
- T → Toxoplasmosis
- C → Colitis (ulcerative) } uses of sulfonamides
  Cardia (nocardia)
- AR → Arthritis (Rheumatoid)

Co - trim - oxazole 00:09:57

- Co(trimethoprim) (Sulfamethoxazole)
- Salient features
  - For right plasma concentration, T:S = 1:5
  - For optimal plasma concentration, T: S = 1:20
- Adverse reactions
  i. Nausea, vomiting, skin rash.
  ii. Folate deficiency → megaloblastic anemia
  iii. Renal failure → uremia
  iv. Rarely → Anemia, neutropenia.
- D.O.C for Co - trimoxazole → "Burping nemo"

  Burp: - Burkholderia cepacea

  Ne: - Pneumocystis jeroveci

  Mo: - Nocardia

  - Sulfonamides on monotherapy, behaves as static agent.
  - Trimethoprim on monotherapy, behaves as static agent.
  - Cotrimoxazole (combination) + Bactericidal agent

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Antibacterial Spectrum

- Sulphonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine. Sensitivity patterns among microorganisms have changed from time-to-time and place to place.
- Those still sensitive are: many Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis (Klebsiella granulomatis), Vibrio cholerae.
- Only a few Staphs. aureus, gonococci, meningococci, pneumococci, Escherichia coli, and Shigella respond, but majority are resistant.
- Anaerobic bacteria are not susceptible. Chlamydia: trachoma, lymphogranuloma venereum, inclusion conjunctivitis, are sensitive, as are Actinomyces, Nocardia and Toxoplasma.

DRUGS FOR PSEUDOMEMBRANOUS ENTEROCOLITIS

Clostridium Difficile Colitis 00:00:21

- Clostridium difficile produces two types of toxins:
  i. Tcd A
  ii. Tcd B
    - Pseudomembranous enterocolitis is the major cause of diarrhoea in hospitalized patients (admitted for more than 3 days)
- Causes:
  - Tetracycline's
  - Clindamycin
  - Cephalosporin's 3rd generation
  - Ciprofloxacin (Fluoroquinolones)
  - **Amoxicillin** – rare cause of Pseudomembranous Enterocolitis
  - **Ampicillin** – most common cause of Pseudomembranous enterocolitis
  - Colitis
  - Most common cause is Ampicillin >3rd Generation Cephalosporin's >Clindamycin >Fluoroquinolones

Treatment 00:03:32

i. Drug of choice is **VANCOMYCIN** (per oral)
It has got increased efficacy against NAP1 strain as compared to Metronidazole

ii. Metronidazole – used in case of mild cases where it is equally effective as Vancomycin expect in pregnancy, children, patient with IBD, patient with intolerance to Metronidazole

iii. Relapse:

- If it is 1st relapse – we have to repeat the course.
- In case of 2nd relapse – we go for 7 week tapering dose of Vancomycin / Fidaxomicin (it is a poorly absorbable macrolide so most of the drug remains in the intestine)
- 3rd relapse – we go for freeze dried capsule of Donor Feces

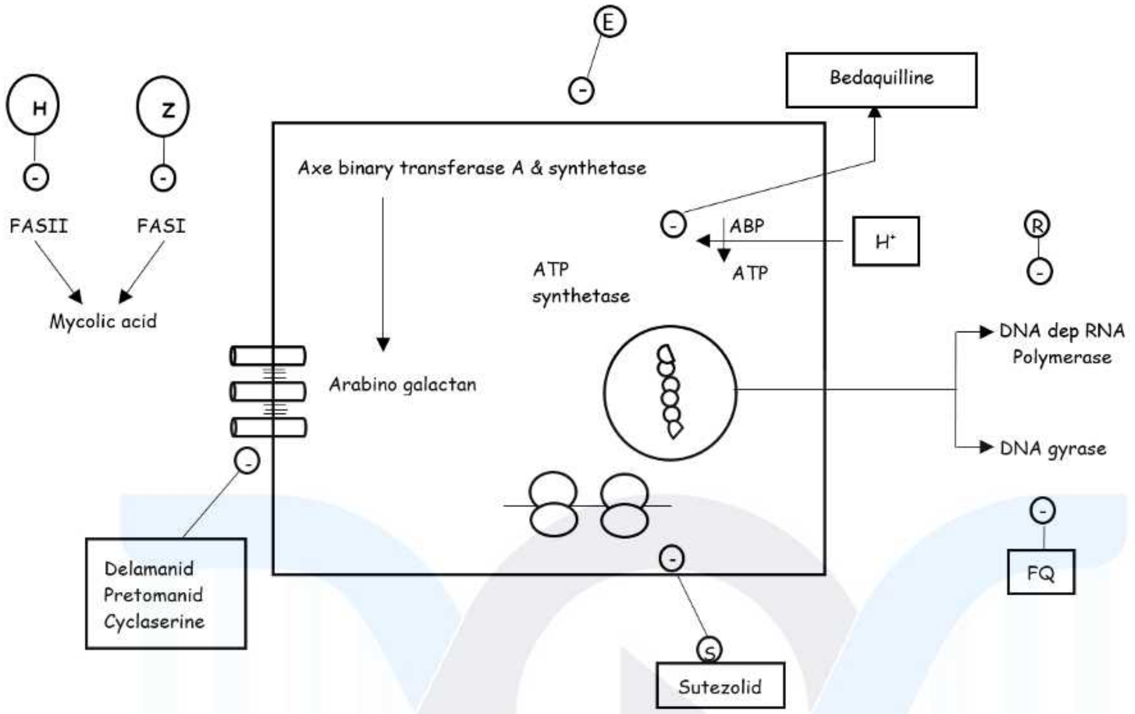
Bezlotoxumab

- It is a monoclonal antibody which is developed against the Tcd B toxin of C. difficile.
- It is less effective than freeze dried capsule of donor feces.

Obiltoxumab

- Drug developed against B. anthracis toxin

ANTI- TB DRUGS


E
-
H
-
FASII
Z
-
FASI
Mycolic acid
Bedaquilline
Axe binary transferase A & synthetase
-
ABP
H⁺
ATP
ATP synthetase
R
-
Arabino galactan
DNA dep RNA Polymerase
DNA gyrase
-
FQ
-
Delamanid
Pretomanid
Cyclaserine
-
S
Sutezolid

CQ/HCQ

Increases Ln entry ↓ Virus infected cells

⊖ Terminal glycosylation ↓ Prevents ACE-R binding with SARS-COV2

Weak base ↓ Concentrated on acid is vesicles ↓ ⊖ Polymerization of Heme

Fatty acid synthase I & II synthesize mycolic acid

- First line:

- Isoniazid → Inhibits fatty acid synthase (FAS-II) II
- Pyrazinamide → Inhibits fatty acid synthase (FAS-I)
- Ethambutol → Inhibits Arabinosyl transferase
- Rifampicin → Inhibits DNA dependent RNA polymerase
- Streptomycin → Inhibits protein synthesis
- Other like -
  - Delamanid
  - Pretomanid (Inhibit cell wall synthesis)
  - Cyclaserine
  - Sutezolid – Inhibits protein synthesis
  - Bedaquilline → Inhibits ATP synthase (QT prolongation)
  - Fluoroquinolones → Inhibits DNA gyrase

Salient features of 1st– line drugs: 00:06:50

- Isoniazid
  - Both intra & extracellular bacilli are acted up on by isoniazid.
  - Acts only on actively dividing bacilli
  - Acts in both acidic / alkaline medium
  - It is a prodrug
  - Converted to active form by catalase peroxidase
  - Active form of isoniazid is converted to its inactive form by acetylation reaction
  - Slow acetylators → drug is accumulated

Toxic effects

i. Drug induced lupus

ii. Peripheral neuropathy (injury pyridoxine)

- Fast acetylators

  ↓

  Drug's effect is mild

  ↓

  Needs increase dosage
- RIFAMPICIN
  - Action on **both Intra & extracellular bacilli**
  - Acts on dormant bacilli/ intermediate diving bacilli
- PYRAZINAMIDE
  - **Acts only on the acidic medium**
  - Mostly acts on intracellular bacilli
  - Ethambutol
  - **The only first line drug that is static (all the first line drugs are Cidal)**
- STREPTOMYCIN
  - Aminoglycoside
  - **Acts only on extracellular bacilli** (as they are positively charged molecules, cannot penetrate)
  - Only parenteral route

Adverse effects 00:12:02

- Difficulty in hearing → streptomycin (ototoxic)
- Dizziness → streptomycin (ototoxic)

- Jaundice (Hepatotoxicity) →
  - Isoniazid (H)
  - Rifampicin (R)
  - Pyrazinamide (Z)

  Z > H > R
- Visual impairment → Ethambutol
- Joint pain → Pyrazinamide (Hyperuricemia)
- Pricking pain (peripheral neuropathy) → pyrazinamide
- Orange/ red color discoloration → Rifampicin
- Purpura/ skin rash → Rifampicin

Regimens for treatment of TB

Type of TB	Intensive phase	Continuation phase
New cases	2 HRZE	4 HRE
Previously treated	3 HRZE	5 HRE

- All the above drugs are administered as Fixed dose combination

- Anti TB drugs.

  a. 1st line

  b. 2nd line
- 2 injectable anti-TB-Drugs.

Antitubercular Drugs

First line drugs:

↓

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Streptomycin

Second line drugs

- Fluoroquinolones:
  - Ofloxacin
  - Levofloxacin
  - Moxifloxacin
  - Ciprofloxacin
- Other oral drugs:
  - Ethionamide
  - Prothionamide
  - Cycloserine
  - Terizidone
  - Paraamino-salicylic acid (PAS)
  - Rifabutin
  - Rifapentine
- Injectable drugs:
  - Kanamycin
  - Amikacin
  - Capreomycin

Treatment:

MDR-TB → If patient is Resistant to isoniazid & rifampicin

Intensive phase
↓
Lasts for 6-9 months
↓
6 drugs
↓
Kanamycin
Levofloxacin
Ethionamide
Cyclaserine
Pyrazinamide
Ethambutol

Continuation phase
↓
Lasts for 18 months
↓
4 drugs
↓
Levofloxacin
Ethionamide
Cyclaserine
Ethambutol

Reserve drugs for MDR-TB

↓

PAS

Capreomycin

Moxifloxacin

XDR-TB → Patient is Resistant to isoniazid + rifampicin + any fluoroquinolone + any aminoglycoside

Intensive phase	Continuation phase
↓	↓
Lasts for 6-9 months	Lasts for 18 months
↓	↓
7 drugs	6 drugs
↓	↓
Capreomycin PAS Moxifloxacin High dose isoniazid Clofazamine Linezolid Amoxyclav	PAS Moxifloxacin High dose isoniazid Clofazamine Linezolid Amoxyclav

Reserve drugs for XDR-TB

↓

Clarithromycin

Thiacetazone ****

(C/I in PL-HIV)

ANTI – LEPROTIC DRUGS

Drugs against mycobacterium leprae 00:00:40

- Sulfone
  - ↓ Dapsone
- Phenazine
  - ↓ Clofazimine
- ATT
  - ↓ rifampicin
  - ethionamide
- Other
  - ↓ Ofloxacin
  - Minocycline
  - Clarithromycin

Dapsone 00:02:03

- Most active drug against M. Leprae
- Purely bacteriostatic agent
- MOA: similar to sulfonamide acts as PABA analogue agents, which inhibits further enzymes necessary for synthesis of tetrahydro folic acid.
- Adverse effects: –

  1.Hemolytic anemia

  2.Methemoglobinemia

  3.G1 upsets

  4.Erythema nodosum leprosum

  5.Peripheral neuropathy

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Clofazimine 00:04:39

- Bactericidal drug
- MOA

1. Anti-inflammatory dye
2. Binds to DNA and presents formation of template for transcription or translation process
3. Generates cytotoxic effects

- Adverse effects
  1. Skin discoloration (red brown to black)
  2. GIT
  3. Upset Red Colored Urine
  4. Eosinophilic Enteritis

Treatment Regimens

Pauci bacillary	Multibacillary
Once in a month	Once in a day
↓	↓
Rifampicin – 600mg Clofazimine-300mg	Dapsone-100mg Clofazimine – 50mg
↓	Daily for 28 days
Administered under supervision for 6 months	Self-administered 12 months

ANTI – MALARIAL DRUGS – I

- Two different hosts for plasmodium—man and mosquito
- Most active stage of replication in humans – merozoites—in hepatocytes and erythrocytes.

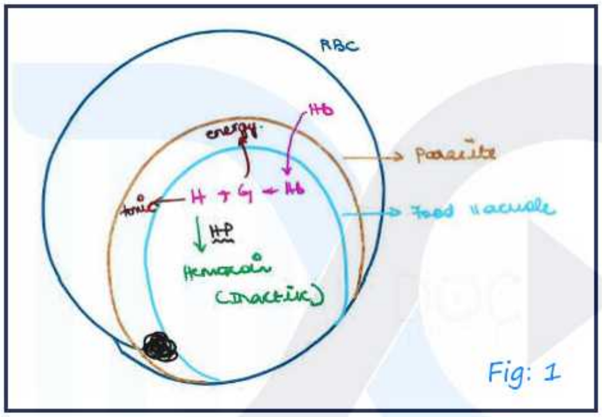

RBC
Hb
energy
Parasite
toxic
H + G ← Hb
Food vacuole
HP
Hemozoin
(Inactive)

Fig: 1

- Hemoglobin is the energy packet for the plasmodium.
- Hb is broken down to heme and globin. Globin is then utilized for energy.
- Heme is toxic to the parasite.
- Heme polymerase enzyme from the plasmodium polymerizes heme to Hemozoin which is an inactive molecule.
- A mitochondrion is also present in the parasite to produce energy for sustenance.

Sites of action of antimalarial 00:05:00

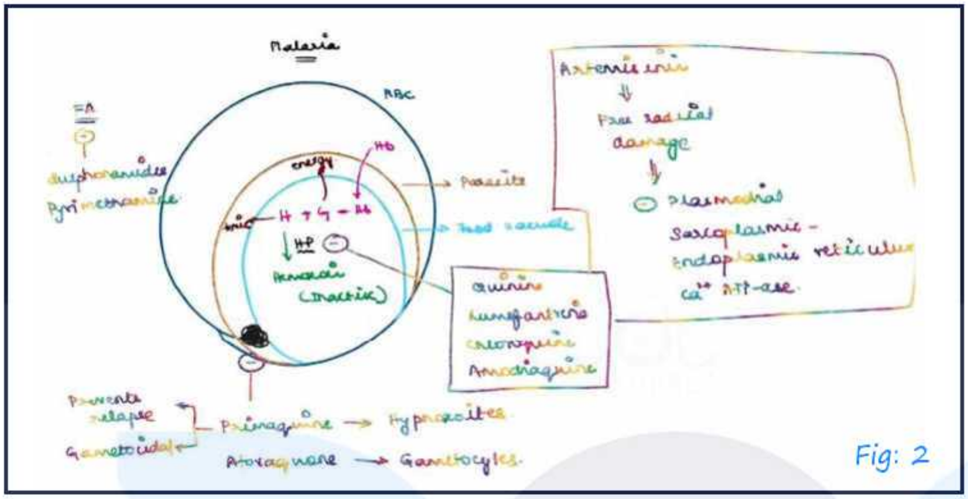

Malaria
RBC
FA
sulphonamides
Pyrimethamine
energy
Hb
mic
H + G – Hb
HP
Hemozoin
(Inactive)
Parasite
Food vacuole
quinine
lumefantrine
chloroquine
Amodiaquine
Artemisinin
Free radical
damage
plasmodial
Sarcoplasmic -
endoplasmic reticulum
Ca++ ATP-ase.
Prevents
relapse
Gametocidal
Primaquine → Hypnozoites
Atovaquone → Gametocytes.

Fig: 2

i. Drugs that block heme polymerase→ quinine, lumefantrine. Chloroquine, amodiaquine.

ii. Drugs that block energy production from mitochondrion → primaquine (also blocks hypnozoites, prevents relapse and is gametocidal), atovaquone.

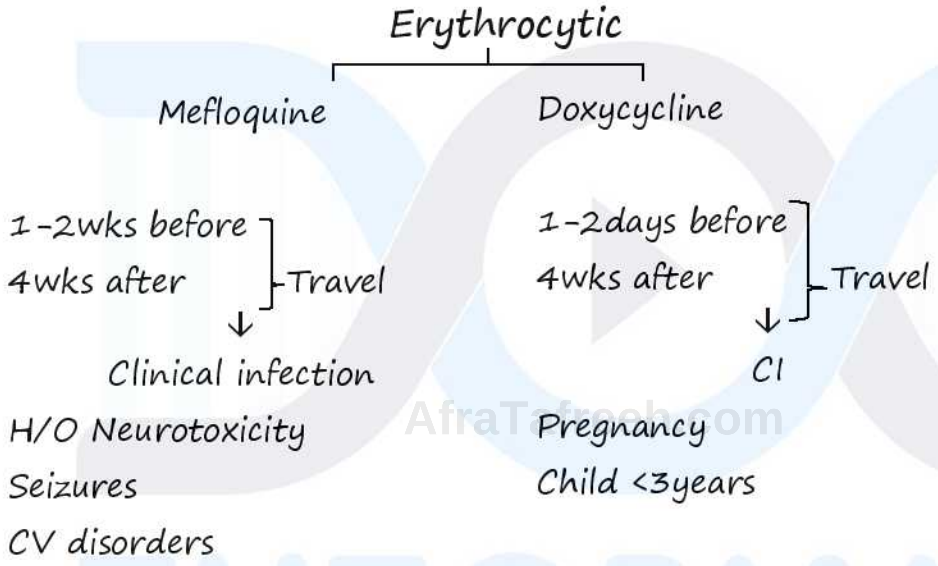
iii. Drugs that block folic acid synthesis → sulphonamides and pyrimethamine.

iv. Inducing free radicle damage → Artemisinin derivative—free radicles produced inhibit Plasmodial Sarcoplasmic Endoplasmic Reticulum Ca2+ Atp Ase.

Treatment regimens

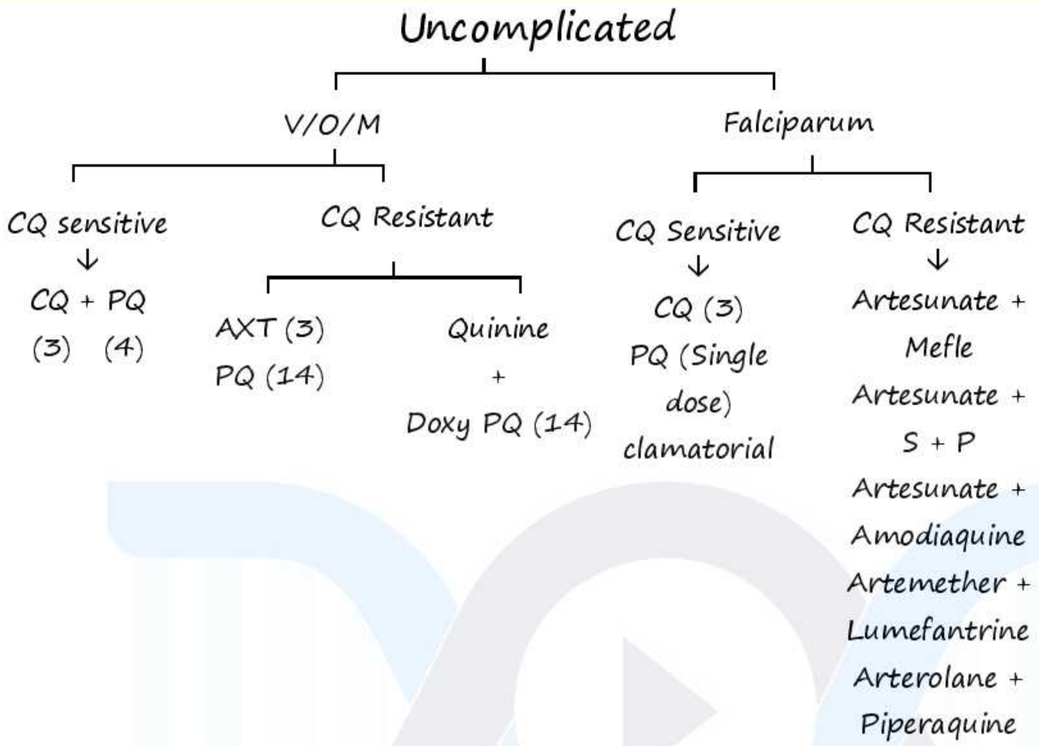
i. **Treating causal prophylaxis**→ to block the pre erythrocytic stage—primaquine (all species).

ii. **Treating suppressive prophylaxis** → for travelers – inhibit erythrocytic stage→ mefloquine and doxycycline. Chloroquine? For CQ sensitive.


Erythrocytic
Mefloquine
Doxycycline
1-2wks before
4wks after
Travel
Clinical infection
H/O Neurotoxicity
Seizures
CV disorders
1-2days before
4wks after
Travel
CI
Pregnancy
Child <3years

- Mefloquine must be **taken 1-2 weeks before, continued during and after 4 weeks after travel, Taken weekly**
- Doxycycline must be taken 1-2 days before, during and after 4 weeks after travel. (**short term traveling**), **once daily 100mg (adults).**
- **Mefloquine is CI in patients with h/o neurotoxicity, seizures, CVA.**
- **Doxycycline is CI in pregnancy and children < 2yrs.**

Clinical Cure 00:11:54


Uncomplicated
V/O/M
Falciparum
CQ sensitive
CQ + PQ
(3) (4)
CQ Resistant
AXT (3)
PQ (14)
Quinine
+
Doxy PQ (14)
CQ Sensitive
CQ (3)
PQ (Single dose)
clamatorial
CQ Resistant
Artesunate + Mefle
Artesunate + S + P
Artesunate + Amodiaquine
Artemether + Lumefantrine
Arterolane + Piperaquine

- Uncomplicated malaria could be due to Plasmodium vivax/ ovale/malarial/ falciparum.
- If the parasite is chloroquine sensitive, we opt for CQ (3 days) + PQ (14 days).
- If the parasite is chloroquine resistant, we opt for Artemisinin combination therapy ACT (3 days) + PQ (14 days) OR quinine + doxycycline combo for 7 days + PQ (14 days).
- **In ACT, Artemisinin + sulfadoxine+ pyrimethamine therapy is not given in vivax/ovale/malarial.**

Falciparum

- If CQ sensitive, prescribe CQ for 3 days (primaquine is not given to prevent relapses falciparum does not have relapse or recrudescence, but it is given because of its gametocidal property). PQ – single dose is enough for its gametocidal property.

If CQ Resistant, Act Is Given

i. artesunate+ mefloquine (CI in cerebral malaria to prevent neuropsychiatric disturbance)
ii. Artesunate + sulfadoxine+ pyrimethamine (not in V/O/M).
iii. Artesunate + amodiaquine
iv. **Artemether+ lumefantrine (DOC in northeastern India)**
v. Arterolane + piperaquine

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- Quinine + clindamycin and doxycycline is also administered in CQ resistance other than the ACT.
- **PQ is given for 14 days to prevent relapse and for gametocidal activity in case of P vivax/ ovale or malarial malaria.**
- **PQ is given as a single dose for its gametocidal property alone in case of P. falciparum malaria.**

ANTI- MALARIAL DRUGS – II

Artemisinin Derivatives

1. Artesunate –it is a water-soluble complex it can be administered by iv/im/po
2. Artemether / artether- it is a lipid soluble complex, it can be administered by im route
3. Arterolane/dihydro artemesinin –administered via per oral route.

Complicated Malaria 00:01:00

i. **Artesunate (iv) or Artemether (im) or arteether (im) followed by P.O ACT**

ii. Quinine (parenteral route) along with dextrose followed by per oral quinine

Malaria During Pregnancy 00:03:15

i. Intermittent preventive treatment in pregnancy (IPTP)

- We administer 1 dose of sulphadoxine + pyrimethamine with folic acid each in 2nd and 3rd trimester.

ii. Pregnant woman Infected with P. vivax - Chloroquine x 3days

- Postpone primaquine until post delivery

iii. Pregnant woman infected with P. falciparum

- If patient is in 1st trimester quinine + clindamycin x7days (Precaution for hypoglycemia as quinine causes hypoglycemia)
- if patient is in 2nd or 3rd trimester ACT x 3days
- Sulphadoxine + pyrimethamine is the slowest acting schizonticide.
- ACT is for 3 days and is the fastest acting schizonticide

Radical Cure 00:07:15

- Drugs inhibiting hypnozoites, prevents relapse.
- Seen with Vivax and Ovale alone

Treatment is 1. Primaquine 0.25mg/kg x14 days

- If the patient is G6PD deficient (G6PD kit assay) primaquine may cause hemolytic anemia, then the dose is 0.75mg/kg once weekly for 8 weeks.
- Tefenoquine - 300micro grams single dose

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Gametocidal drugs 00:09:45

i. Primaquine

ii. Quinine

Primaquine can be used against all species

- 0.25mg/kg in case of Vivax, ovale or malarial for 14 days (radical+ gametocidal)

- In case of falciparum, it is a single dose having gametocidal properties
- Quinine can be used as a gametocidal drug against only Vivax/ ovale/ malarial

Chloroquine 00:12:05

- It is a rapid acting agent.
- It has got a very high volume of distribution (retina involvement may cause Bulls eye retinopathy)
- Adverse effects:
  - Most common nausea, vomiting, headache
  - On prolonged use there might be development of bull's eye retinopathy
  - May cause ototoxicity
  - Greying of hair
  - QT prolongation (caused by mefloquine, chloroquine, quinine)

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Contraindications/ Drug Interactions

1. Mefloquine
2. Amiodarone
3. Antiarrhythmic agents

Other Uses of Chloroquine

Mnemonic: RIP MLA

- Rheumatoid arthritis

- Infectious mononucleosis
- Porphyria cutanea tarda
- Photogenic reactions
- Malaria (vivax/Ovale/malarial)
- Lepra reaction
- Lupus erythematosus (SLE &DLE)
- Amoebiasis (systemic)

Quinine 00:16:42

- **Drug of choice for 1st trimester of pregnancy.**
- L-isomer is used in the treatment of malaria.
- Monotherapy does not prevent recrudescence. Doxycycline or clindamycin prevents recrudescence but doxycycline is contra indicated in pregnancy.

Adverse Reaction

- If administered by per oral route it has got a bitter taste.
- Causes **hypoglycemia** so administered in iv along with dextrose
- It causes **increase in acid secretion**
- It causes ototoxicity or oculo-toxicity
- Patient may develop **cinchonism (ringing of ears)**
- **Hemoglobinuria (black water fever)**
- **Nephrotoxicity**

Lumefantrine

- It is administered along with highly fatty food.
- It inhibits cytochrome CYP2D6

Amodiaquine

- It causes Hepatotoxicity and agranulocytosis

Mefloquine

- Causes neuro toxicity

Primaquine

- If administered in G6PD deficient individual, it produces hemolytic anemia
- Primaquine can be administered with food

Clindamycin

- Can be administered in children and pregnancy
- It is drug of choice for aspirational pneumonitis in children

Artemesinin Derivatives

- Gametocidal property seen only against early-stage gametes, it is not seen with mature gametes, this is why it is given along with primaquine.

ANTI HELMINTHIC AGENTS

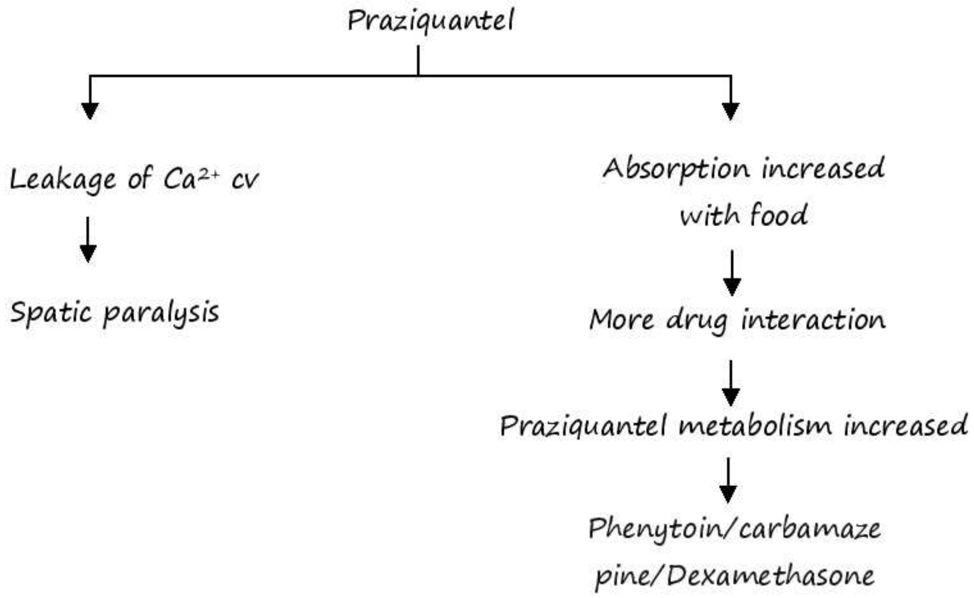
Albendazole 00:00:56

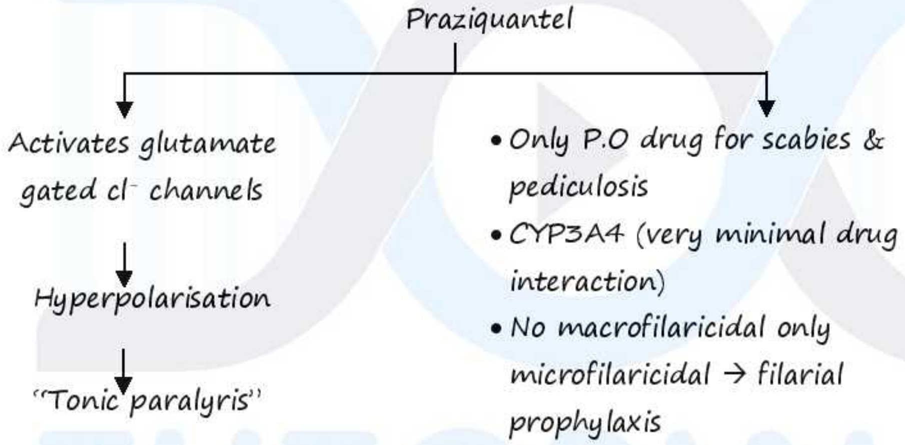
Albendazole

MOA concentration of action	**PK (Pharmacokinetics)**	**Salient features**
- Binds & - β tubulin of parasite - Glucose uptake	- Has active sulfoxide metabolic - Tissue vermicaidal activity - Fasting route for intestinal worms - **Fatty meal for Neurocysticercosis, Hydatid cyst, cutaneous larva migrans** - Steroids → increases absorption of Albendazole	- Less active against → tritons trichurid (mebendazole > albendazole) → Filariasis (as an adjunct) - No drug given for ocular cysticercosis - **CI in pregnancy caution in hepatic/renal failure**

ADVANTAGE

- Hepatotoxicity (thiabendazole > Albendazole)


Praziquantel
Leakage of Ca²⁺ cv
Spatic paralysis
Absorption increased with food
More drug interaction
Praziquantel metabolism increased
Phenytoin/carbamazepine/Dexamethasone


Praziquantel
Activates glutamate gated cl⁻ channels
Hyperpolarisation
"Tonic paralyris"
• Only P.O drug for scabies & pediculosis
• CYP3A4 (very minimal drug interaction)
• No macrofilaricidal only microfilaricidal → filarial prophylaxis

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Dec (Diethyl Carbinamine)

- Slow acting microfilaricidal
- Not effective against microfilaria in nodules & transudate
- Chronic lymphatic obstruction

  ↓

  Not affected by DEC
- Filariasis

Mebendazole

- > albendazole (tricturis)

- In high dose

  ↓

  Produce adverse reactions

  ↓

  - **Hypersensitivity**
  - **Alopecia**
  - **Granulocytopenia**

Pyrantel Pamoate

- Spastic paralysis
- No action against trichuris
- E.g. of tasteless vermicidal agent

Piperazine

- Flaccid paralysis

  ↓

- CI in RF/epilepsy
- Safe in pregnancy

Levamisole

- Inhibit carbohydrate metabolism

  ↓

- Famurate reductase
- Immune modulatory
- "Drugs which does not excite ascaris"

  ↓

  - Pyrantal palmaote
  - Piperazine

Albendazole/Mebendazole

- All nematodes
- Neuro cysticercosis
- Echinococcus
- Trichuris Trichura

Praziquantel 00:08:22

- All flukes
- Tapeworm

Ivermectin 00:11:07

- Strangyloides stercoralis
- Onchocerciasis
- Filarial prophylaxes

- DEC
  - Filariasis
  - B. malayi
  - B. Timori
  - Loaloa infections
- NITAZOXANIDE
  - Cryptosporidium
  - Resistant ciardiasis
  - Ivermectin
- Therapeutic use of each drug ...Where used? can be represented in a tabular form as well.

Choice of drugs for helminthiasis		
Worm	First choice drugs	Alternative drugs
1. Roundworm Ascaris lumbricoides	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole Ivermectin
2. Hookworm Ancylostoma duodenale Necator americanus	Pyrantel, Mebendazole, Albendazole Mebendazole, Albendazole	Levamisole Pyrantel
3. Pin worm Enterobius (Oxyuris) vermicularis	Pyrantel, Mebendazole, Albendazole	Piperazine
4. Thread worm Strongyloidiasis stercoralis	Ivermectin	Albendazole
5. Whipworm Trichuris trichiura	Mebendazole	Albendazole
6. Trichinella spiralis	Albendazole	Mebendazole
7. Filaria	Diethyl carbamazine,	Albendazole

Wuchereria bancrofti. Brugia malayi	Ivermectin	
8. Cutaneous larva migrans Ancylostoma caninum	Albendazole	Ivermectin
9. Tapeworms Taenia saginata Taenia solium Hymenolepis nana Neurocysticercosis	 Praziquantel Praziquantel Praziquantel Albendazole	Niclosamide, Albendazole Niclosamide, Albendazole Niclosamide, Nitazoxanide Praziquantel
10. Hydatid disease Echinococcus granulosus, E multilocularis	 Albendazole Albendazole	Mebendazole

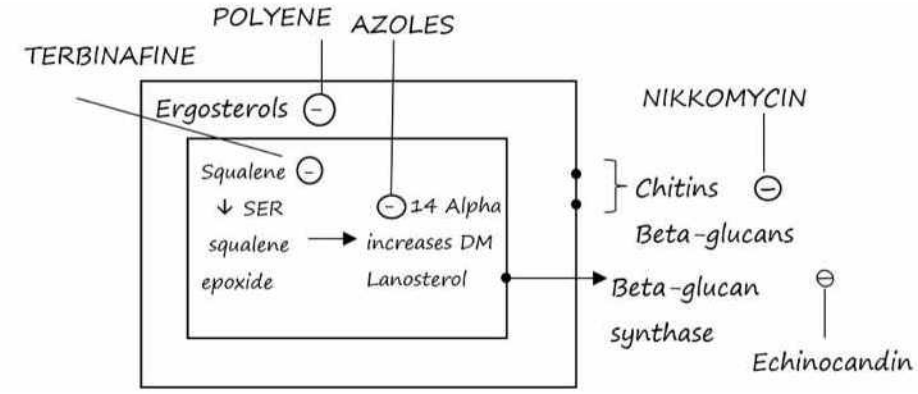
ANTI-FUNGAL AGENTS PART-I

- Azoles and Amphotericin-B combinational is irrational because azoles inhibit ergosterol formation, so, there is no scope for binding of Amphotericin-B to the ergosterol
- Squalene converted to Squalene Epoxide by Squaline epoxide reductase enzyme
- Squalene Epoxide converted to Lanosterol
- **Lanosterol converted to Ergosterol by 14 – alpha D-Methylase enzyme**
- Nikkomycin – new drug inhibiting Chitins
- SER inhibited by Terbinafine
- 14 alpha D-Methylase enzyme inhibited by Azoles
- Beta-glucan synthase inhibited by Echinocandin

CELL WALL INHIBITORS – NIKKOMYCIN

CELL MEMBRANE INHIBITORS – POLYENES

Mechanism of action 00:03:34


POLYENE
AZOLES
TERBINAFINE
Ergosterols ⊖
Squalene ⊖
↓ SER
squalene epoxide
⊖ 14 Alpha
increases DM
Lanosterol
NIKKOMYCIN
Chitins ⊖
Beta-glucans
Beta-glucan synthase
⊖
Echinocandin

DRUGS ACTING WITHIN THE CELLS

i. Mitosis → Inhibited by GRISEOFULVIN

ii. Protein synthesis → inhibited SORDARIN

iii. Nucleic acid synthesis → Inhibited by FLUCYTOSINE

(Flucytosine acts as a primer of 5-Fluro Uracil)

(entry of drug into the cell is the essential step)

- Combination of flucytosine with Amphotericin-B; Amphotericin-B causes cell damage and it paves a way for the entry of flucytosine in to the cell of fungus

Polyenes 00:08:32

- Polyenes

↓

Binds to the sterol

↓

Leakage of intracellular ions/enzymes (forming artificial pores)

↓

Fungicidal

Amphotericin- B- Spectrum of Action

00:09:33

- Broad spectrum anti-fungal & therapeutic uses of AMB

Antifungal Spectrum

- Amphotericin B is either fungicidal or fungi static, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma Capsulatum, Cryptococcus, neoformans. Coccidioides, Immitis, Blastomyces dermatitidis, and many strains of Aspergillus. (Note: Amphotericin B is also used in the treatment of the protozoal infection leishmaniasis.)

Amphotericin-B

- Absorption ↓
  - i. Poor from gut (iv infusion)
  - ii. T ½ - 15 days ↓ Effect persists Even after excretion
- Distribution ↓
  - Extensive distribution to tissues
- Dose ↓
  - Low for candida – Not given for superficial candidiasis
  - + immune stimulators (G. SCF GM-CSF)

↓ Adverse drug Reaction

i. Renal impairment (reversible) → prevention → adequate hydration

ii. Hypokalemia/Hypo magnesia → distal renal tubular acidosis

iii. Febrile reactions → prevention → hydrocortisone administration

iv. BMD (Bone marrow depression)

Newer Amphotericin-B Analogues

i. Ambisone (Amphotericin B in lipid bilayer)

ii. Abelcet (AB lipid complex)

iii. Amphocil (AB in colloid dispersion)

- Less toxicity (Nephrotoxicity) ↓ DOC in renal impairment
- High doses ad mistered Rapidly & safely ↓ Conventional amphoteriecin-B → Gradual dose escalation

Nystatin 00:15:58

- Only topical
- High systemic toxicity

ANTI-FUNGAL AGENTS PART - II

Azoles 00:00:15

Azoles

Imidazole
↓
Ketoconazole/
miconazole/
clotrimazole/
tioconazole

Triazole → Preferred
↓
Voriconazole/
fluconazole/
itraconazole/
Posaconazole

- Triazoles → preferred → Because
  1. Greater selectivity
  2. Better CNS penetration
  3. Resistant to degradation
  4. Less endocrine disturbances

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Imidazoles → (MOA)	Triazoles
Inhibit fungal oxidative enzyme i. Lethal accumulation of H_2O_2 ii. Decreases ergosterol synthesis	Inhibit lanosterol 14 Alpha demethylase i. Decreases ergosterol synthesis ii. Lethal accumulation of sterol precursors

- Therapeutic indications of imidazole's & Triazoles
  - Epidermophyton, Macrospore, Trichophyton, Candida, and Malassezia.

Ketoconazole 00:04:50

Ketoconazole

Absorption ↓ Good absorption ↓ But absorption decreased in alkaline PH

Distribution ↓ Wide distribution ↓ But decreases CNS penetration

Metabolism ↓ CYP3A4 ↓ More drug interactions

Least selective

↓ also

Inhibits sterol synthesis in humans also

Side effects

- Gynecomastia
- Loss of libido

Uses

- Decreases bone pain in advanced androgen dependent ca. prostate

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Other Side Effects

- Pruritis
- Photophobia

- Hepatotoxicity
- Disulfiram like reaction

Tioconazole → Fungal nail infection

Isocnazole
Fenticonazole } Vaginal Candidiasis

VORICONAZOLE

Absorption	Distribution	Cross resistances
↓	↓	↓
Good/Rapid Not affected by PH	Wide Also distributed to CNS	Between voriconazole & itraconazole

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- Synergism with ampo B → as pergillus infection
- Vi → visual disturbances
- Vigabatrin
- Ivabradine
- Voriconazole

Side Effects

1. Most Common: Rash
2. Transient visual disturbances

   ↓

   Altered visual perception

   ↓

   Visual hallucination
3. Cyclodextrin (additive) → hypo Na^+

4.Dose reduced in hepatic failure

- **POSACONAZOLE**
  ↓
  - Highest P.O bioavailability
  - No dose reduction in Heart or renal failure
  - Structure similar to litraconazole
  - Static → Candida infections
  - Cidal → Aspergillus infections

FLUCONAZOLE → Doc

- Candida
- Coccidioidal meningitis

ITRACONAZOLE → Doc

- Endemic mycoses
- Sporotrichosis

VORICONAZOLE → Doc

- Invasive aspergillosis

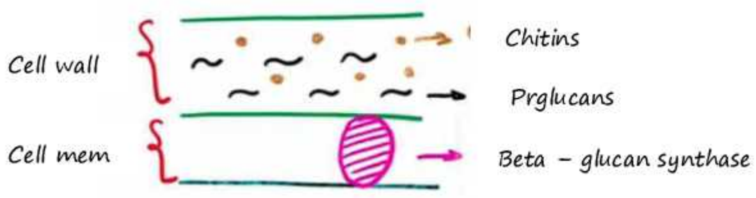
POSACONAZOLE → Doc

- Fungal infections in graft vs host disease

TERBINAFINE → Doc

- Dermatophytes

Echinocandins 00:16:20



- Chitins inhibited by Nikkomycin
- Beta – glucan synthase inhibited by Echinocandins
- Increased susceptibility osmotic of fungal cell

1. CASPOFUNGIN → cannot be given P.O do not cross BBB (only iv route) (increased risk of infusion related reactions)
2. MICAFUNGIN → not effective in aspergillosis
3. ANIDULAFUNGIN

Adverse Effects –

- Acute → infusion related (because given via parenteral route)
- Hypo K^+
- Organ toxicity

USES

1. Deep & invasive (candidiasis)
2. Esophageal candidiasis
3. Salvage therapy for invasive aspergillosis
4. Febrile neutropenia in immunocompromised patients

- Pneumocystis jirovecii

  ↓

- Doc: co-trim-oxazole

  2nd line agents

  ↓

  1. Primaquine +clindamycin
  2. Dapsone/trimethoprim
  3. Pentamidine (replaced by other drugs due to below side effects)
     - Hypo/ hyperglycemia
     - Hypo Na^+
     - Nephrotoxicity with azotemia
  4. Atovaprone
  5. Prednisolone

ANTI VIRAL DRUGS

Anti-viral drugs

- Viruses are the most difficult to treat pharmacologically because they are able to adapt and modify.
- Broad spectrum anti-viral drugs unlike broad spectrum anti-bacterial drugs are rare due to rate of developing resistance in viruses being high.

Herpes Infection 00:01:46

i. ACYCLOVIR

- It is prodrug
- It is converted to its active form inside the body after three phosphate groups are attached to it.
- Acyclovir $\xrightarrow{\text{Herpes specific thymidine kinase}}$ Acyclovir monophosphate $\xrightarrow{\text{cellular kinase}}$ Acyclovir triphosphate.
- Acyclovir triphosphate acts as substrate for viral DNA polymerase and hence inhibits viral replication
- Enzyme Thymidine kinase necessary for activation of Acyclovir is only produced in virus infected cells therefore other healthy cells are not harmed
- Order of Acyclovir activity is a follows

  HSV 1 > HSV 2 > HZV = EBV
- No teratogenicity has been observed with Acyclovir.

- Acyclovir produces crystals which induce renal failure by tubular obstruction
- Acyclovir has short $t_{1/2}$ and has to be **administered 5 times/day**
- Viruses develop resistance by modifying thymidine kinase structure and inhibiting Acyclovir activation

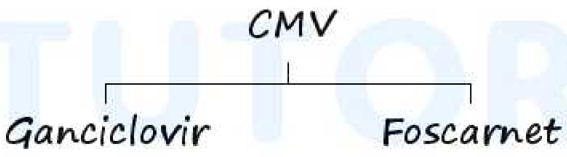
ii. VALACYCLOVIR

- It is a prodrug which is converted to active form Acyclovir
- It is long acting

iii. FAMCICYCLOVIR

- It is a prodrug converted to active form pencicylovir
- Pencicylovir can be used **topically for labial herpes**

CMV



a. GANCICLOVIR

- It has poor per oral bioavailability.
- A prodrug is used to improve bioavailability called valganciclovir.
- Valgancicyclovir is **used to treat CMV retinitis.**
- Both Gancicyclovir and Valgancicyclovir are used together to treat immediate sight threatening CMV retinitis,
- Gancicyclovir is administered as Ocular implants.

- Adverse effects
  - i. Neutropenia } Bone Marrow Depression (BMD)
  - ii. Thrombocytopenia }
  - iii. Fever
  - iv. Seizures (when given with Imipenem)
- "**BMD" is the Dose Limiting Toxicity (DLT)**

b. Foscarnet

- Given when Gancicyclovir is contra indicated.
- Also to treat Acyclovir Resistant Herpes/CMV
- Adverse effects.
  - i. Hypocalcemia
  - ii. Hypomagnesemia
  - iii. Nephrotoxicity (**Direct tubular toxicity**)
  - iv. Contact Dermatitis (genital ulcers)
- When drug is excreted in urine some drug may get deposited in the genital area causing contact dermatitis.
- Remember - CAR, CMV, CMN

CAR	CMV	CMN
↓	↓	↓
FosCARnet	used to treat CMV	Adverse effects Hypocalcemia Hypomagnesemia Nephrotoxicity

- Newer drugs for CMV are cidofovir and fomivirsen.
- Cidofovir is cytidine analogue used topically

- Cidofovir is contra-indicated in renal failure and no need for thymidine kinase

Hepatitis + RSV 00:14:52

RSV

Ribavirin Palivizumab

i. Ribavirin
  - Synthetic oligonucleotide
  - Given orally/inhalational
  - Drug of choice to treat chronic hepatitis C along with $IFN\alpha_2b$
  - Does not cross BBB but crosses blood placental Barrier
  - Cannot be used to treat viral encephalitis.
  - Teratogenic in nature
  - It may cause hemolytic anemia.

ii. Palivizumab
  - "mab" indicated it is a Monoclonal Antibody.
  - It's a monoclonal Antibody against Fc protein on RSV which is a surface protein
  - It inhibits the entry of the virus into the cell
  - Palivizumab is given intra muscularly every month.
  - Adverse effect may include anaphylaxis

IFN (α, β, γ)

- IFN $\alpha_2 b$
  - a. Used to treat hepatitis B
    - Other drugs for hepatitis B
      - i. Lamivudine
      - ii. Tenofovir
  - b. Contraindicated in Decompensated liver disease
  - c. 2 effects

Direct ↓ On uninfected Cells

Undirect ↓ acts as immune suppressant

- IFN$\alpha_2 b$ acts on uninfected cells and induces production of enzymes which prevent further infection.
- IFN$\alpha_2 b$ has anti-cancer/anti-proliferative property.

- Anti-cancer property is used to treat
  - CML
  - RCC
  - Hairy cell leukemia
  - Kaposi sarcoma
  - Condyloma acuminata
- Adverse effects
  - Depression
  - Anorexia
  - Bone Marrow Depression

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Direct Acting Agents (DAA) for Hep-C

- NS3 protease inhibitors
  - ↓ Drug name includes 'previr'
- NS 5A inhibitors
  - ↓ Drug name include 'tasvir'
- Polymerase inhibitor
  - Nucleoside analogue
    - ↓ Sofosbuvir
  - Non-Nucleoside analogue
    - ↓ Dasabuvir

- Hepatitis
  - C virus treatment
    - a. 1st line → Ribavirin + IFN $\alpha_2 b$
    - b. 2nd line
      - Sofosbuvir + Daclatasvir in non-cirrhotic patients
      - Sofosbuvir + Velpatasvir in cirrhotic patients

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Drugs used for influenza

Drugs used for influenza

Hemagglutinin inhibitor

(for Influenza A)

↓

- Amantadine
- Rimantadine

(more potent)

↓

- Rimantadine is a derivative of Amantadine

↓

Adverse effects

- livedo reticularis
- CCF because of fluid overload
- newer drugs like baloxavir marboxil inhibit mRNA synthesis

Neuraminidase inhibitor

(for Influenza A, B and Avion)

↓

- 'mivir' drugs

↓

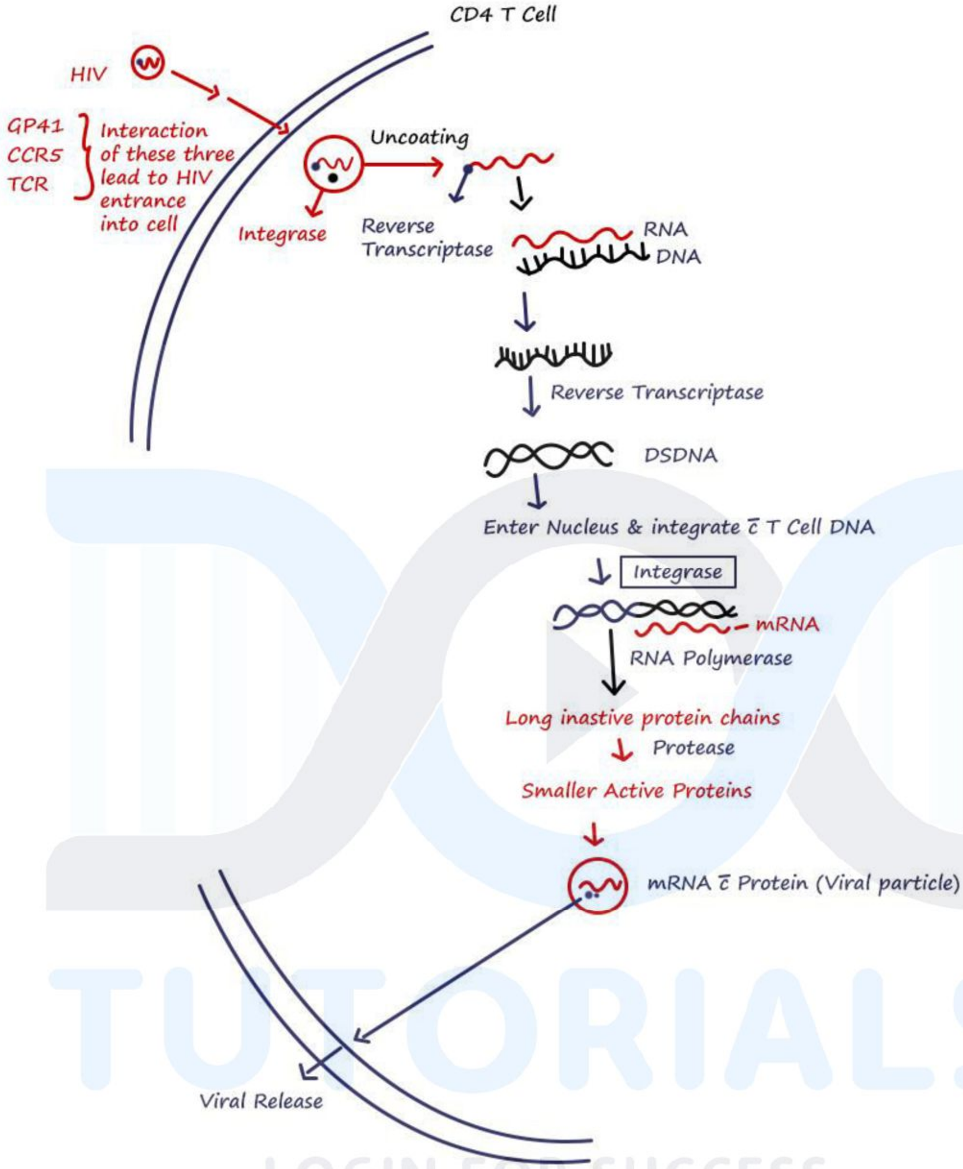
- Oseltamivir
- Zanamivir
- Peramivir

↓

Zanamivir causes Broncho constriction

- Newer drug against Influenza – BALOXAVIR MARBOXIL – inhibits mRNA synthesis

ANTI-RETROVIRAL DRUGS


CD4 T Cell
HIV
GP41
CCR5
TCR
Interaction of these three lead to HIV entrance into cell
Uncoating
Integrase
Reverse Transcriptase
RNA
DNA
Reverse Transcriptase
DSDNA
Enter Nucleus & integrate c̄ T Cell DNA
Integrase
mRNA
RNA Polymerase
Long inastive protein chains
Protease
Smaller Active Proteins
mRNA c̄ Protein (Viral particle)
Viral Release

long inactive protein chains

Drugs 00:08:30

1.Entry inhibitors

GP41 inhibitors: Enfuvirtide

CCR5 inhibitors: Maraviroc

TCR inhibitors (MAB): Ibalizumab

2.Nucleoside / Nucleotide reverse transcriptase inhibitors: - (NRTI)

- Nucleoside RTI: -
  - Dine
  - Bine
  - Sine

  They need to be converted to triphosphate in order to become active

  Abacavir
- Nucleotide RTI: Tenofovir → It should be converted to diphosphate to become active.

  (i.e No need of virus specific thymidine kinase)

3.Non-nucleoside reverse transcriptase inhibitor (NNRTI)

These drugs are noncompetitive irreversible reverse transcriptase inhibitors

End with – VIR

4.Integrase inhibitor – Tegravir

5.Protease inhibitor – Navir

6.Pharmacokinetic enhancer: Cobicistat (No antiviral activity) → (Inhibit CYP3A) → leading increase concentration of antiviral drugs

HAART 00:14:38

Entry inhibitors:

1.Enfuvirtide: given by S/C route (GP41 inhibitor)

↓

Peptide

Therefore, not given by per oral route

Note: semaglutide: Is a peptide but can be given perorally

2.Maraviroc: CCR5 inhibitor

No activity against CXCR5 (Trofile assay: - will give information about receptor involved) i.e CCR5 (or) CXCR

3.Ibalizumab:

- T cell receptor MAB
- IRIS (Immune reconstitution inflammatory syndrome)

  ↓

  Treatment steroids

  No need to stop therapy, unless it is life threatening

NRTI

Zidovudine:

- Available as capsules, syrup, IV preparations
- Competitive inhibitor of stavudine
  - Therefore, both should not be given at same time
  - Both cause lipodystrophy
  - Mitochondrial toxicity (Maximum lactic acidosis)

    ↓

    Highest with stavudine
- High CNS penetration (therefore given in HIV associated neuro cognitive disease)

Adverse effect:

1. Bone marrow depression: seen in high doses

   With ganciclovir

   With IFN α

2. Toxic myopathy
3. Hepatic necrosis with lactic acidosis (Rare)

NRTI → Lamivudine

- Long intracellular T1/2
- Drug reduced in renal failure
- Not combined with emtricitabine

  Adverse drug reaction

  - Most common headache
  - Lactic acidosis
  - Hepatomegaly with steroids (rare)

Tenofovir

- 2 forms
  - Tenofovir disoproxil fumarate: More renal toxicity (Fanconi)
  - Bone demineralization (More in patients with DM (HTN)
  - Tenofovir alafenamide

    ↓

    High intracellular T1/2

    Less renal / Bone toxicity
- Not given with adefovir

Abacavir

- Hypersensitivity reaction in people with HLA B5701 allele)
- Stop therapy (No rechallenge)

NNRTI 00:24:50

  - VIR -

- Used only in HIV Type 1 infection
- Metabolized by CYP 450, therefore lot of drug interactions
- T1/2 > NRTI, since irreversible inhibitor
- If resistant to any one NNRTI than only etravirine can used no other NNRTI can be used

  Etravirine Least cross resistance.

Efavirenz

- Cross resistance with nevirapine
- Adverse effect:
  - Most common rash
  - Neurological adverse drug effects
    (Prevention: Taken before sleep)
    Therefore, given during night
- Not given with high fatty meal

Nevirapine

- Relatively safe in pregnancy
- Antiretroviral prophylaxis for infants borne to mother living with HIV – 1 only
- Adverse effects:
  - Rash, hepatitis
  - Adverse reactions ∝ CD4 count

    Therefore, contraindicated in

    Female with $CD_4 > 250$ / µl

    Male with $CD_4 > 400$ / µl

Protease inhibitors 00:29:00

– Navir –

- Given in combination
- CyP3A4 inhibitor (more with ritonavir)

Ritonavir Boosting: It inhibits CYP3A4 and thus increasing duration of action of other antiretroviral drugs

- Now cobicistat issued in place of ritonavir

Note

In PLHIV with TB → Avoid rifampicin – since microsomal inducer.

Use rifamycin / Rifabutin

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Adverse effects of PI's

- GI side effects
- Pancreatitis
- Hyperglycemia
- Lipodystrophy
- Atazanavir
  - Arymptomatic, reversible, unconjugated hyperbilirubinemia.
  - Also associated with cholelithiasis (Rare)
- Indinavir: Nephrolithiasis

Integrase inhibitors

Tegravir.

- Dolutegravir:

  Contraindicated with

  - Antacids
  - Calcium preparations

  Contraindicated in pregnancy: - increase risk of neural tube defects

- Raltegravir – associated with

  1.Rhabdomyolysis

  2.Hepatic failure

  3.SJS

Newer drugs 00:33:30

- Cabotegravir: Integrase inhibitor

  Route: IM

- Rilpivirine: NNRTI

  Can be given via intramuscular route

- Fastemsavir: Entry inhibitor (GP 120)

  Peroral route

Regimen 00:34:53

Initial regimen for most people with HIV

- Bictegravir / Tenofovir / emtricitabine

  ↓

  (Contraindicated in pregnancy)

- Dolutegravir / Abacavir / lamivudine

  ↓

  HLAB5701 – Negative

  Without chronic HBV co-infection

- Dolutegravir + (Emtricitabine / Lamivudine) + Tenofovir

  ↓

  Renal toxicity

  Bone toxicity

NACO 2019

First-line ARV Regimen guidance

ART Regimen	Recommended For
Tenofovir + Lamivudine + Efavirenz	First line ART regimen for: All ARV naïve PLHIV patients with HIV-1 infection, age>10 years and body weight > 30 kg
Abacavir + Lamivudine + Efavirenz	First-line ART regimen for all patients with abnormal serum creatinine values – Refer to ART guidance for special situations. All adults and adolescents with body weight less than 30kg
Tenofovir + Lamivudine + Lopinavir/ ritonavir	First-line ART regimen for: All women with single dose Nevirapine exposure in a past pregnancy; All confirmed HIV-2 or HIV-1 & HIV-2 co-infection
Zidovudine + Lamivudine + Nevirapine Zidovudine + Lamivudine + Efavirenz	All patients who are on either of these first-line regimens initiated earlier in the programme need to be continued on the same regimen unless failing.

- Before giving abacavir 5701 allele should be analysed

Recommended PEP regimens

Dosages of the drugs for PEP for adults	Recommendation for PEP	Duration
Tenofovir (TDF) 300 mg + Lamivudine (3TC) 300 mg one tab (FDC) once daily (1-OD)	One tab immediately within 2 hours of accidental exposure, either at day time or at night time	Next day one tab once OD, continue for 4 weeks
Lopinavir (200 mg) + Ritonavir (50 mg) Two tab (FDC) twice daily (2-BD)	Two tab immediately within 2 hours of accidental exposure, either at day time or at night time	Next day two-tab BD, continue 4 weeks.
If LPV/r is not available/ can not be used, Tenofovir (300 mg) + Lamivudine (300mg) + Efavirenz (600 mg), One tab OD may be given for 4 weeks.		

ART regimens in pregnant and breastfeeding with HIV

Target population	Drug regimen	Remark
Pregnant and breastfeeding women in HIV (ART Naïve/ "Not already" receiving ART)	TDF+3TC+EFV	FDC of TDF (300 mg) + 3TC (300 mg) + EFV (600 mg) – to be given 2 hours after low fat or fat free dinner
Pregnancy and breast feeding women with HIV already receiving ART	The same ART regimen must be continued	E.g. If they are already on AZT+3TC+ NVP/EFV, continue the same regimen
ART regimen for pregnant women having prior exposure to NNRTI for PPTCT	TDF+3TC and LPV/r	FDC of TDF (300mg) + 3TC (300mg) – 1-tab OD and FDC of LPV (200 mg/r (50 mg)-2-tab BD

- Efavirenz should not be given with high fat diet

Opportunistic infections 00:43:06

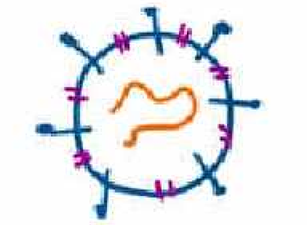
Pneumocystis jiroveci / Toxoplasmosis

- Co-trim (Trimethoprim) oxazole → Sulfamethoxanol (If CD4 < 350)
- If allergic → Dapsone
- Stop if CD4 > 350 on 2 different occasions 6 monthgs apart.

Cryptococcal meningitis:

- Fluconazole
- Stop if CD4 >200.

ANTI-VIRAL DRUGS (ANTI – COVID DRUGS)



Structural proteins
↓
Spike protein
(−)
Griffithsin
Umifenovir

Non - Structural proteins
↓ (−) Lopinavir/Ritonavir

1. 3-CT like protease
2. Papain like protease
3. Helicase – (−) Triazoles bananas
4. RdRp:
   (−)
   Remdesivir
   favipararir
   Galidesivir

Hydroxychloroquine/Chloroquine 00:04:33

CQ/ HCQ

↑ ZN entry
↓
Virus infected cells

(−) Terminal glycosylation
↓
Prevents ACE – R Binding I SARS-COV2

Weak bases
↓
Concentrated on acidic vesicles
↓
(−)
Polymerization of heme

Pharmacokinetics

Metabolites → 1. Des – ethyl HCQ (major)
2. Des ethyl CQ
3. Bi – des ethyl HCQ

Absorption t1/2 ↓ 3-4hrs

Terminal t1/2 ↓ 40-50 days (High volume distribution)

Excretion

Urine

Adverse effect

1.Brain → Suicidality

2.Eyes → Irreversible retinal damage → Discontinue Rx
↓
Monitor (Annal)
Visual acuity
Central 24° VF
Spectral Domin OCT

3.Cardiac

Muscle heart
↓
AV block
Pulmonary HTN
Sick sinus syndrome
QT prolongation

4.Liver failure/Renal failure → Caution

5.Blood → Life threatening hypoglycemia
Aplastic anemia/Agranulocytosis
- Discontinue Rx

6.Muscle → Proximal myopathy/neuropathy

7.Skin → Aggravate psoriasis (polyuria)

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Drug interactions:

(+)
Mefloquine
↓
Epileptogenic

↑ Effects of
1. Digoxin
2. Insulin
3. Cyclosporin
4. QT prolonging agents

↓ Effects of
1. Anti-epileptics
2. Praziquantel
3. Ampicillin

CQ → (-) Topoisomerase II
↓
Genotoxic effect
↓
CI: Pregnancy
Nursing women
Children

Hydroxychloroquine/Chloroquine 00:04:33

- Macrolide antibiotic
  ↓
  Anti-Viral

1. Ebola
2. Zika
3. RSV
4. HINI
5. Entero
6. Rhino

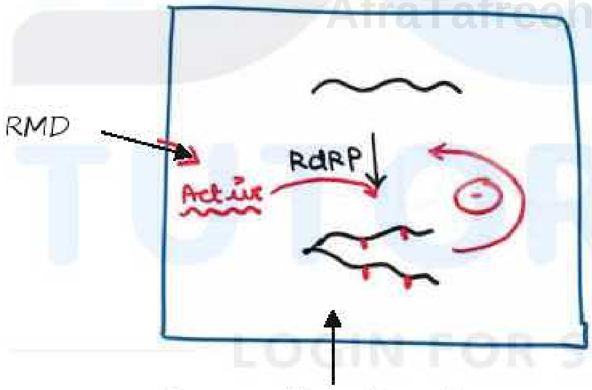
→ Azithromycin – 1. ↑ Type I & III interferons
↓ 2. Activates viral recognition genes MDA 5 & RIG I
(-) Viral entry

A/E

OLID – Pneum
↓ ↘ Diarrhea → Motilin receptor agonist
Ototoxic ↘
↓ Liver toxicity
Reversible ↓
Cholestatic
Jaundice

Remdesivir (IV) 00:20:06

- Tried for: Ebola Marbury nipals SARS-COV2
- Prodrug of C – Adenosine → Phosphonamidite adenosine nucleotide
- Structurally similar to Tenofovir alafenamide



Corrected by Ribonuclease
(EXON)

PK:

1. Plasma t1/2 → 1hr ← Rapidly metabolized by plasma hydroxylase
2. Plasma t1/2 of active metabolic → 24hrs
   ↘ Excreted by – Urine
3. Phosphoramidate → High first pass metabolism → PE

4.Fast acting →

Natural nucleotide → Monophosphate

↓

Triphosphate

CQ/HCQ

↑

RMD → (Bio isotere of monophosphate) (-)

Triphosphate

↓

Bypasses rate limiting step

5.On rapid I.V → ↓ BP/Cardiac arrest/Death

↓

Over 60min

Adverse effect

- Nausea vomiting
- Constipation headache
- Anemia lymphopenia
- Hyperglycemia
- Infusion related reaction
- Renal Failure (CI if CGFR < 30ml/min)
- CI vasopressors (End organ failure)

Favipiravir – Per oral

- Broad spectrum anti-RNA viral agents → No effect on DNA viruses
- (-) Replication

↓

Influenza A ⎤
Influenza B ⎦ Neuraminidase inhibitor resistance
Avian
Ebola
Lassa
Sars-Cov2

Pro-Drug
↓ Intracellular Phosphoribosylation
Active F-RTR → Removed by
Recognized as purine nucleotide
↓
hydroxylation by:

(-) RNA
Dependent RNA
Polymerase

1. Aldehyde oxidase
2. Xanthine oxidase
↓ CI in Gout
Excreted in urine

Adverse effects

1. Teratogenic
2. Bone marrow depression
3. ↑ Liver enzymes
4. Diarrhea

Ribavirin

Intracellular
↓
Ribavirin monophosphate
↓
Ribavirin triphosphate

$$\text{Inosine 5 phosphate} \xrightarrow{\text{IMPDH}} \text{Xanthosine 5 phosphate}$$

↓
↓ Intracellular GTP
↓
(-) RNA replication

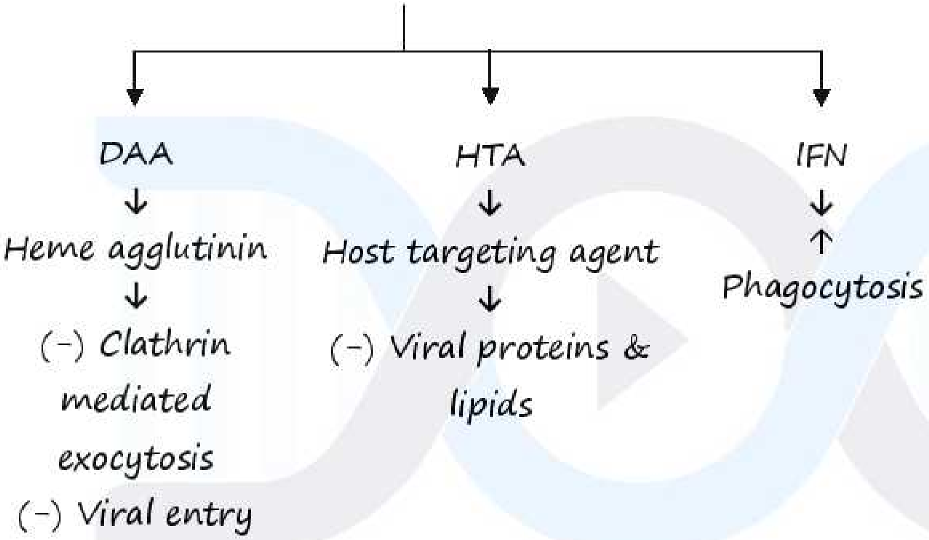
Adverse effect

- Severe anemia at high doses

- Drug interaction with warfarin

Umifenovir

- Broad spectrum virucidal (Enveloped/Non enveloped) (DNA/RNA virus)
- Tried with Favipravir
- Excreted unchanged in urine → Long t1/2 ~ 25hrs



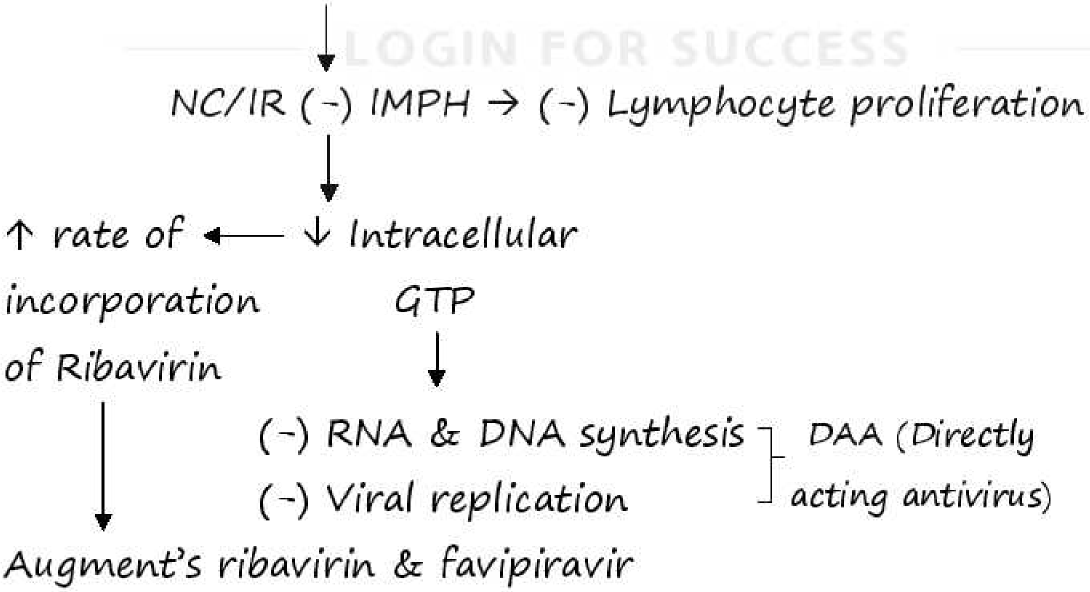
DAA ↓ Heme agglutinin ↓ (–) Clathrin mediated exocytosis (–) Viral entry

HTA ↓ Host targeting agent ↓ (–) Viral proteins & lipids

IFN ↓ ↑ Phagocytosis

Merimepodib (P.O)

- Anti – Hepatitis C drug



↓

NC/IR (–) IMPH → (–) Lymphocyte proliferation

↓

↑ rate of incorporation of Ribavirin ← ↓ Intracellular GTP

↓

(–) RNA & DNA synthesis
(–) Viral replication
] DAA (Directly acting antivirus)

Augment's ribavirin & favipiravir

Adverse effect

- Fatigue, Nausea, vomiting, diarrhea

Rintatolimod (I.V)

↓

Synthetic double stranded RNA

↓

Agonist at Toll – like – Receptor 3

- Does not level of IFN

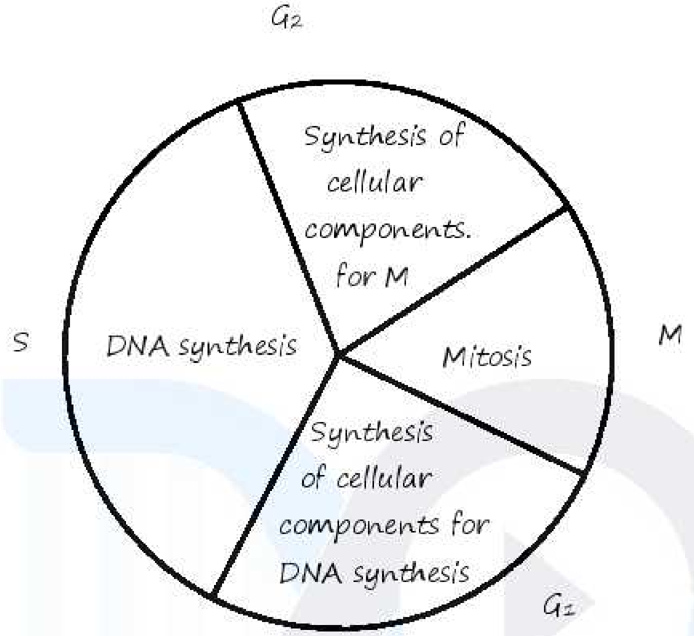
  1.Tocilizumb – Anti – IL – 6 antibodies

  2.Vitamin C/D → (-) Inflammatory response (RAAS)

  (+) Anti-microbial peptides (Human cathelicidin)

CELL CYCLE KINETICS AND RESISTANCE

Cell cycle 00:01:55

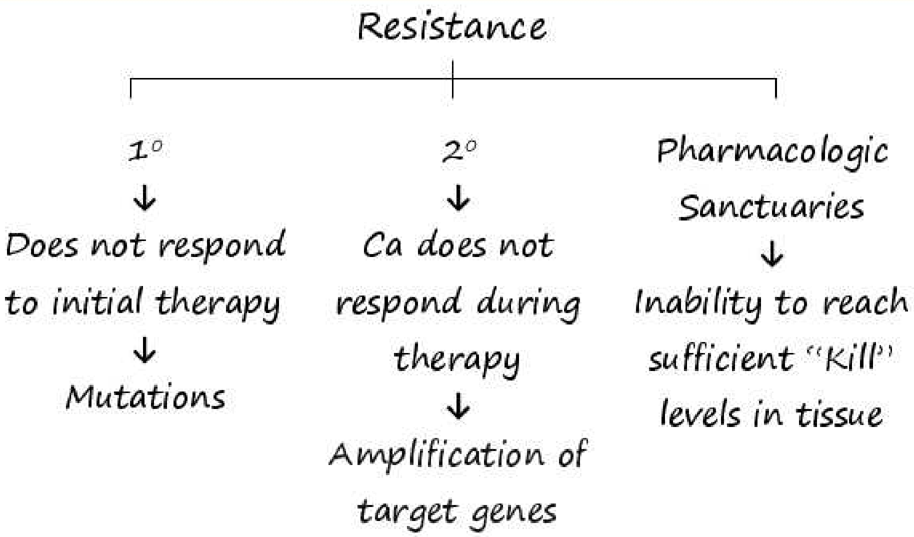

G_2
Synthesis of cellular components. for M
S
DNA synthesis
Mitosis
M
Synthesis of cellular components for DNA synthesis
G_1

Cells cycle kinetics 00:05:06

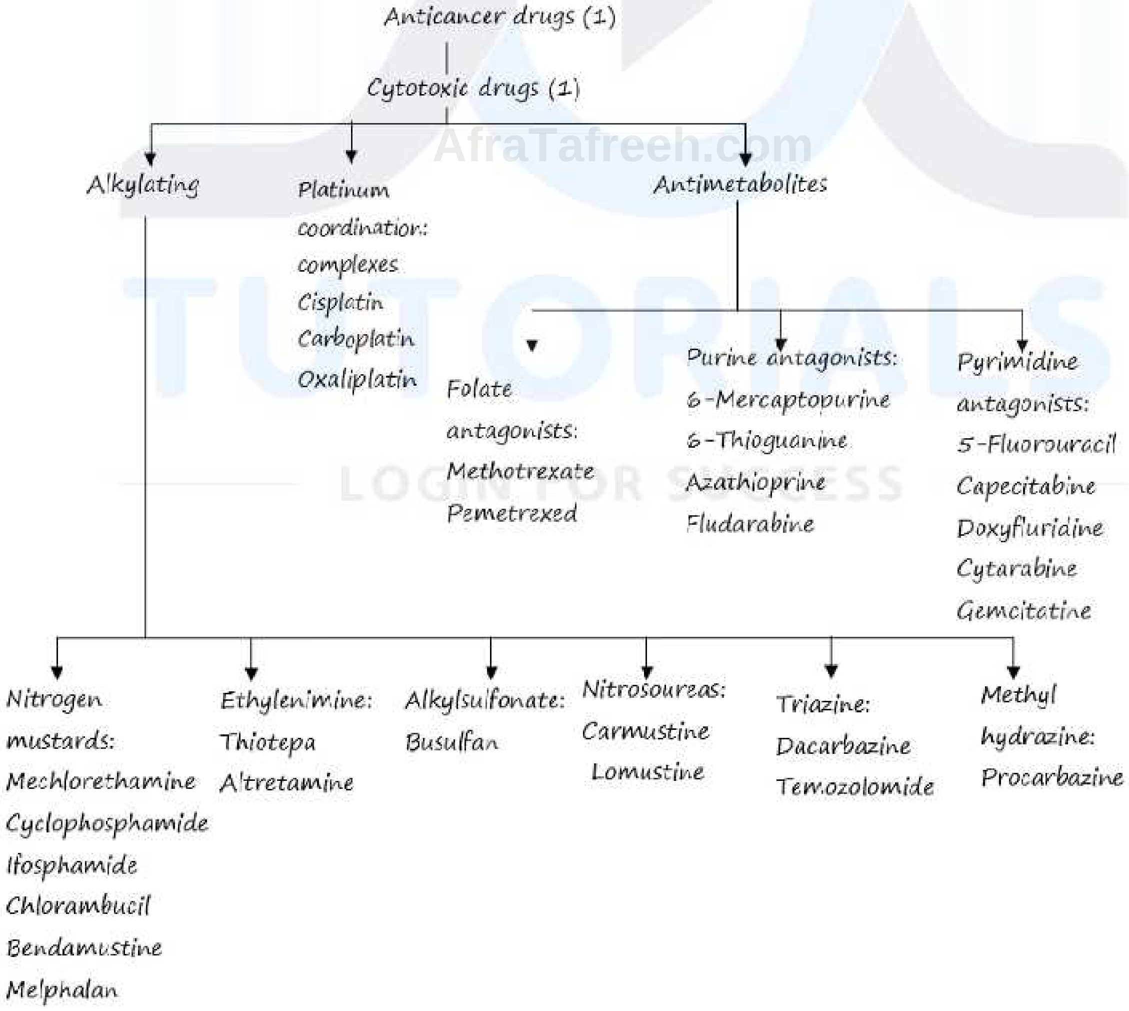
Cells cycle kinetics

Cell cycle specific	Cell cycle non-specific
↓	↓
S → Antimetabolites	- Alkylating agents
Irinotecan	- Anti – tumor antibiotics
Histone DA inhibitor	- Nitrosoureas
G_2 → Bleomycin	
M → Vinca alkaloids	
Taxanes	
Estramusline	

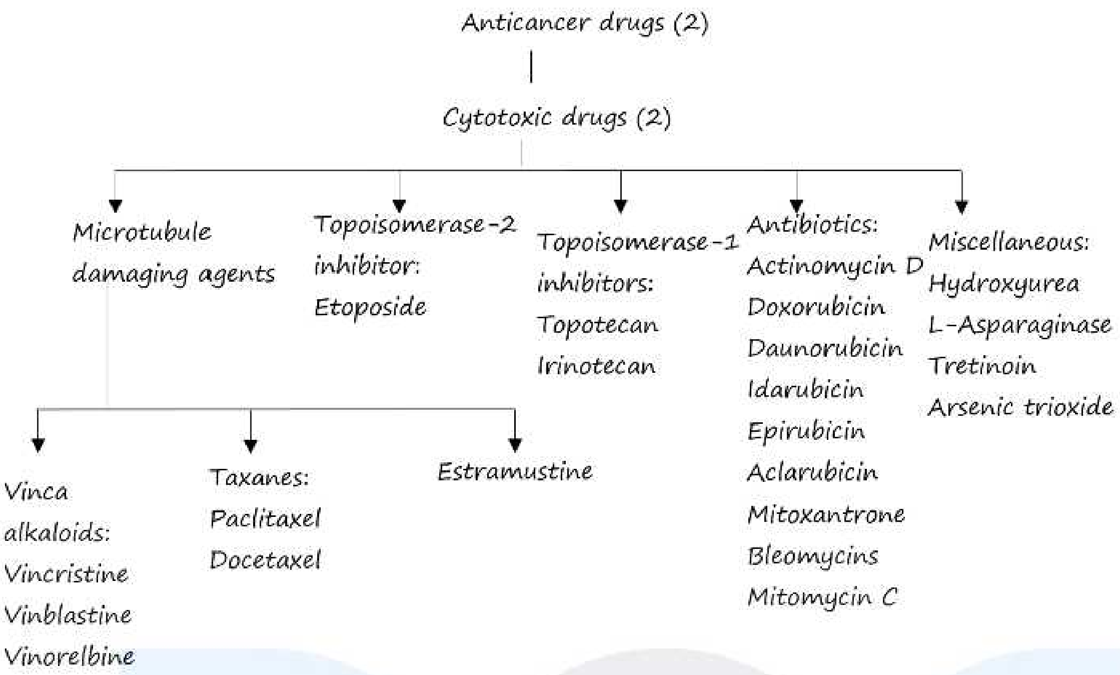
Resistance 00:08:39

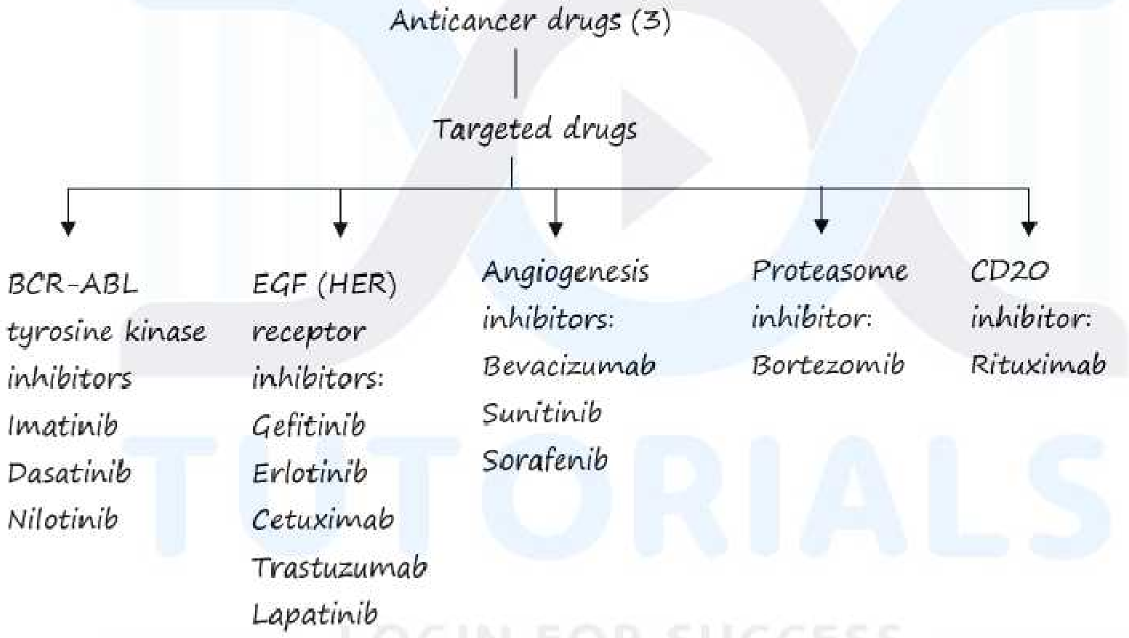

Resistance
1°
Does not respond to initial therapy
Mutations
2°
Ca does not respond during therapy
Amplification of target genes
Pharmacologic Sanctuaries
Inability to reach sufficient "Kill" levels in tissue

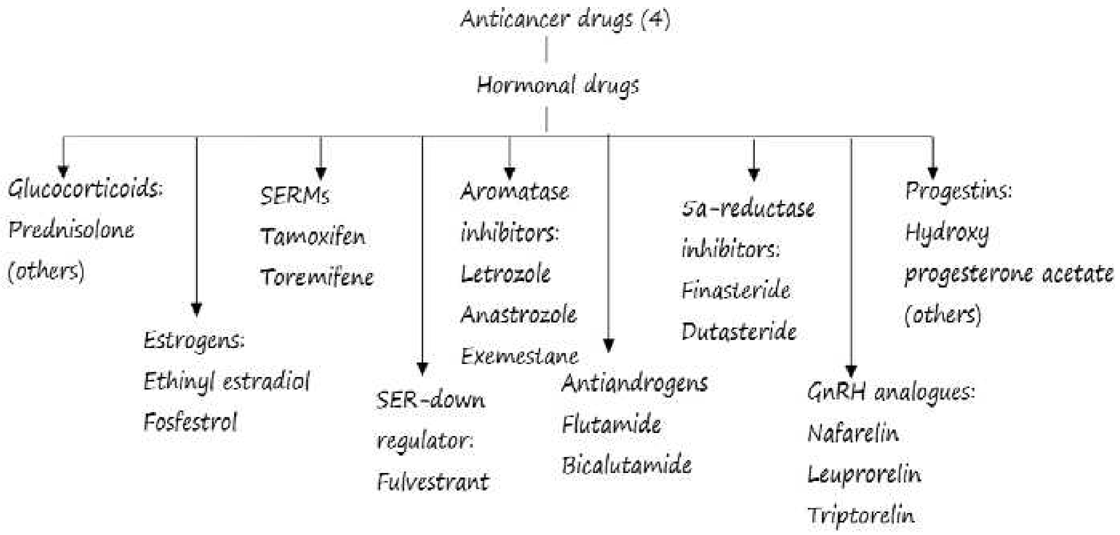
- Classification (overall) of antineoplastic drugs


Anticancer drugs (1)
Cytotoxic drugs (1)
Alkylating
Platinum coordination: complexes
Cisplatin
Carboplatin
Oxaliplatin
Antimetabolites
Folate antagonists:
Methotrexate
Pemetrexed
Purine antagonists:
6-Mercaptopurine
6-Thioguanine
Azathioprine
Fludarabine
Pyrimidine antagonists:
5-Fluorouracil
Capecitabine
Doxyfluridine
Cytarabine
Gemcitatine
Nitrogen mustards:
Mechlorethamine
Cyclophosphamide
Ifosphamide
Chlorambucil
Bendamustine
Melphalan
Ethylenimine:
Thiotepa
Altretamine
Alkylsulfonate:
Busulfan
Nitrosoureas:
Carmustine
Lomustine
Triazine:
Dacarbazine
Temozolomide
Methyl hydrazine:
Procarbazine

DOC TUTORIALS
LOGIN FOR SUCCESS


Anticancer drugs (2)
Cytotoxic drugs (2)
Microtubule damaging agents
Topoisomerase-2 inhibitor: Etoposide
Topoisomerase-1 inhibitors: Topotecan Irinotecan
Antibiotics: Actinomycin D Doxorubicin Daunorubicin Idarubicin Epirubicin Aclarubicin Mitoxantrone Bleomycins Mitomycin C
Miscellaneous: Hydroxyurea L-Asparaginase Tretinoin Arsenic trioxide
Vinca alkaloids: Vincristine Vinblastine Vinorelbine
Taxanes: Paclitaxel Docetaxel
Estramustine


Anticancer drugs (3)
Targeted drugs
BCR-ABL tyrosine kinase inhibitors Imatinib Dasatinib Nilotinib
EGF (HER) receptor inhibitors: Gefitinib Erlotinib Cetuximab Trastuzumab Lapatinib
Angiogenesis inhibitors: Bevacizumab Sunitinib Sorafenib
Proteasome inhibitor: Bortezomib
CD20 inhibitor: Rituximab


Anticancer drugs (4)
Hormonal drugs
Glucocorticoids: Prednisolone (others)
Estrogens: Ethinyl estradiol Fosfestrol
SERMs Tamoxifen Toremifene
SER-down regulator: Fulvestrant
Aromatase inhibitors: Letrozole Anastrozole Exemestane
Antiandrogens Flutamide Bicalutamide
5a-reductase inhibitors: Finasteride Dutasteride
GnRH analogues: Nafarelin Leuprorelin Triptorelin
Progestins: Hydroxy progesterone acetate (others)

ALKYLATING AGENTS

Alkylating agents 00:00:11

Alkylating Agents

- All iv drugs ↓ Powerful vesicants ↓ Tissue necrosis on extravasation
- All cause ↓ Leucopenia
- Dose (dose limiting toxicity) ↓ BMD (dose marrow depression)
- It with xeroderma pigmentosa ↓ Highly sensitive to alkylating agents

DOT TUTORIALS
LOGIN FOR SUCCESS

MOA 00:01:32

- Contain an electrophilic core

↓

- Forms reactive molecular species

↓

- Covalently binds & alkylates N_7 position of guanine

↓

- Cross linking of base pairs
- Abnormal base pairing
- DNA strand breaks
- At N-2 position → Trabectedin

Cyclophosphamide 00:04:29

Cyclophosphamide (pro drug) $\xrightarrow{CYP2B6}$ Active form

Phosphoramine mustard

↓

Toxic to Cancer cells

↓

i. Cardiac & pulmonary fibrosis
ii. SIADH
iii. Thrombocytopenia (cyclo < mechlorethamine)

Acrolein

Hemorrhagic cystitis

(Side effects)

↓

i. Ifosfamide > cyclophosphamide
ii. Prevention by vigorous hydration → MESNA

DOC – MESNA

Rx of choice – vigorous hydration

USES

i. Leukemia (CLL)
ii. NHL (non-Hodgkin's lymphoma)
iii. Neuroblastoma
iv. Lupus nephritis/arteritis
v. Good pasture syndrome

MECHLORETHAMINE

- Powerful vesicant

↓

- Treatment: inj. Thio sulfate
- Reveal latent viral infections (herpes)

Platinum Compounds 00:09:20

- MC → iv
- Cisplatin
- Carboplatin
- Oxaliplatin

Uses

- Treatment:
  - Ovarian ca
  - Advanced colorectal ca (oxaliplatin)

Side Effects

- Vomiting
- Oto/hemato/neuro/nephrotoxicity → cisplatin

↑

With oxaliplatin

PROCARBAZINE

- Can be given via P.O
- CSF positive penetrate BBB
- Brain tumors treatment

Side Effects

- Most leukemogenic agent
- Inhibit MAO, can precipitate Serotonin Syndrome
- Disulfiram like reaction

- No cross resistance with any alkylating agent with procarbazine

Busulfan

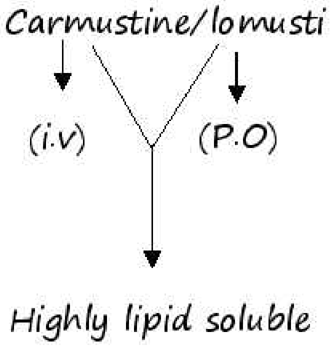
Side Effects

- Adrenal insufficiency
- Pulmonary fibrosis (busulfan lung)
- Skin pigmentation

Drugs Causing Pulmonary Fibrosis

- "NICE BABE"
- Ni → Nitrofurantoin
- CE → Cyclophosphamide
- B → Busulfan
- A → Amiodarone
- B → Bleomycin
- E → Ergot & derivatives (methysergide, Bromocriptine, Cabergoline)
- Ergot derivatives, Busulfan & Cyclophosphamide tend to produce cardiac & pulmonary fibrosis.

CARMUSTINE/LOMUSTINE


Carmustine/lomusti
(i.v)
(P.O)
Highly lipid soluble

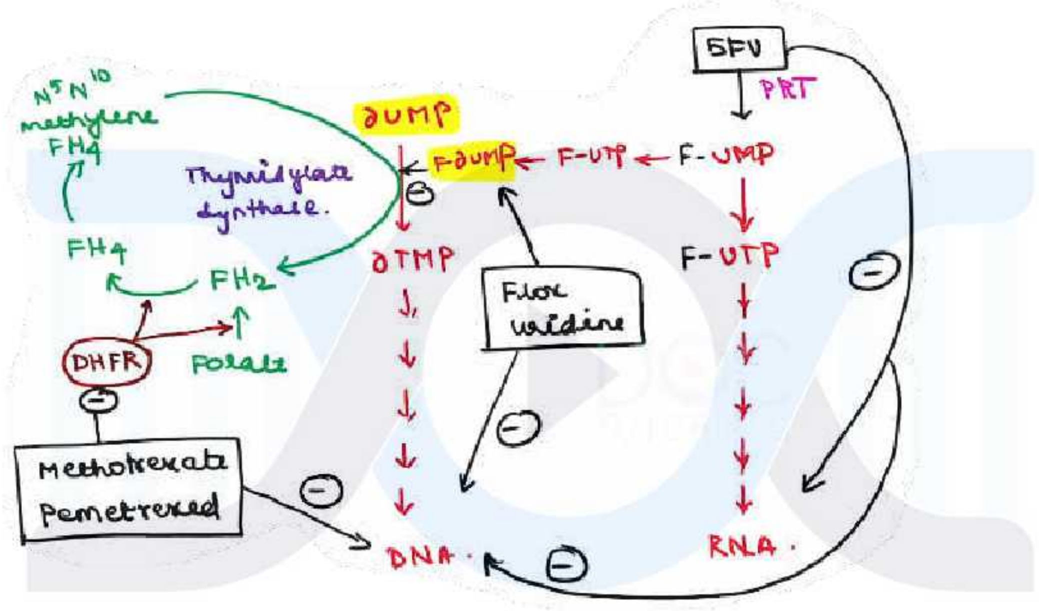
- Cross BBB can be used in brain tumors
- Somestine → Renal failure
- Temozolamide → Doc → For brain tumors (malignant glioma & astrocytoma)

DOC TUTORIALS
LOGIN FOR SUCCESS

ANTI METABOLITES

- "S" Phase specific agents.
- DLT → bone marrow suppression (dose limiting toxicity)

MOA:


N^5N^{10} methylene FH4
Thymidylate synthase.
FH4
FH2
DHFR
Folate
⊖
Methotrexate
Pemetrexed
⊖
dUMP
FdUMP
⊖
F-UTP
F-UMP
5FU
PRT
dTMP
Floxuridine
⊖
F-UTP
⊖
DNA.
⊖
RNA.

5FU

PRT

F – UMP → F-UTP → FdUMP → Inhibits thymidylate synthase PRT – Phosphoribosyl transferase

F – UTP
↓
↓ → 5FU inhibits both RNA and DNA synthesis
↓
↓
RNA → Methotrexate inhibits only DNA syn
→ Floxuridine - inhibit only DNA synthesis

Methotrexate 00:07:00

Methotrexate

Folic acid analogue
↓
forms polyglutamate derivatives
↓
Anti-cancer action

Uses

i. ALL
ii. Choriocarcinoma
iii. Osteogenic sarcoma
iv. DMARD in rheumatoid arthritis
v. Ectopic pregnancy

i. Toxicity of methotrexate

Administer Glucarpidase (MTX cleaving enzyme)

ii. MC adverse effects

Alopecia

Headache

Mucositis → R_x – **Palifermin (keratinocyte growth factor)**

iii. BMD (bone marrow depression)

N^5N^{10} Formyl FH_4 can be administered
↓
AKA as **leucovorin/Folinic acid** converted to N^5 N^{10} methylene FH_4
↓
Decreases BMD

- Folinic acid/leucovorin rescue → in R_x of BMD.

iv. Renal toxicity → Crystaluria
↓

7-OH metabolite
↓
Adequate hydration
Urinary alkalinization

PEMETREXED 00:13:40

↓

- ⊖ Purine & pyrimidine synthesis & glycinamide ribonucleotide formyl transferase enzyme
- Uses –
  - Combined with cisplatin
    ↓
    R_x: – Mesothelioma
- Uses
  - Non-small cell lung carcinoma (NSCLC)
- Adverse effects
  - BMD
  - hand and foot syndrome
- R_x
  - Dexamethasone
  - Cobalamine
  -

CYTARABINE 00:15:43

↓

- Most 'S' phase specific
- ⊖ Inhibit DNA polymerase enzyme
- Given only via iv infusion

- Short t½

5-FLURO URACIL 00:16:35

SFU

F – dUMP
↓
Incorporated on DNA
↓
– DNA synthesis
↓
Competitive reversible inhibition of thymidylate synthase

F – UTP
↓
Incorporated RNA
↓
– RNA synthesis

- 5FU
  - → can be given via → iv/topical
  - → Good CNS penetration (cross BBB)
- Uses
  - i. Colorectal Ca
  - ii. Anal Ca
  - iii. Premalignant keratosis & Superficial BCC } Topical route

- 5FU also acts as radio sensitizer

6MP & 6TG 00:19:20

6MP	6TG
↓	↓
Analogue of hypoxanthine	Analogue of Guanine
↓	↓
Converted to	Converted to
↓	↓
G-thio IMP	G-thio GMP

⊖Nucleotide metabolism

	6MP	6TG
Uses: –	ALL	ALL & AML
	↓	↓
Adverse effects	BMD, hepatotoxicity, G1 dis,	Squamous cell Ca of skin (SCC)

- In 6MP
  - Allopurinol dose must be reduced when administered with 6-Mercapto Purine.
  - Dose reduction is not necessary in 6TG
- SCC
  - Rx: – **CEMIPLIMAB**

Cladribine 00:22:50

- Adenosine analogue

  ↓

  IV infusion
- Hairy cell leukemia

- Waldenstrom macrogliobulinemia

Fludarabine

- Induces Apoptosis
- **Synergistic effect with cyclophosphamide**
- Uses
  - CLL, NHL, AML, ALL

NATURAL PRODUCTS

β – Tubulin 00:01:00

β – Tubulin

Polymerization
↓
Assembly inhibitors
Vinca alkaloids
↓
i. Blastine → leucopenia (marker for therapeutic effect)
ii. Cristine → ass with severe constipation
iii. Vinorelbine → neurotoxicity (cristine>relbine>blastine)
↓
Vinca alkaloids
↓
SIADH (vinca > cyclophosphamide)

Depolymerization
↓
disassembly inhibitors
↓
Taxanes
↓
i. Paclitaxel → hypersensitivity reactions
ii. Docetaxel – edema
iii. Nab – paclitaxel → water soluble (administered via parenteral route)
↓
Produce peripheral neuropathy (stocking & glove neuropathy)

DOC TUTORIALS
LOGIN FOR SUCCESS

- Camptothecin → Topotecan → inhibits Topo I ← Irinotecan

Topotecan ↓
- Renal elimination
- BMD

Irinotecan ↓
- Hepatic elimination
- Diarrhea (Rx Racecadopril)
Delayed secretory diarrhea

ADVERSE EFFECTS OF CYTOTOXIC (ANTI CANCER) DRUGS AND ITS MANAGEMENT

General adverse effects 00:00:15

- Hyper uricemia
  - Allopurinol (dose reduction when administered along with cisplatin)
  - Rasburicase (tumor lysis syndrome)
- Radiation induced xerostomia
  - Amifastins
  - Pilocarpine (increases secretion of saliva)
- Hypercalcemia
  - Zolendronate
  - Pamidronate
- Anemia
  - Epoietin α
  - Darbopoietin α
- Neutropenia
  - G-CSF → filgrastin
  - GM – CSF → sargramostin
- Thrombocytopenia
  - Eltrombopag
  - Oprelvelin (IL-11)
- Nausea/vomiting
  - Early vomiting due to → (immediately) → because of stimulation of $5HT_3$ receptors

- Delayed vomiting
  ↓
  After 2 days
- For early vomiting → $5HT_3$ $\ominus$ → - Setron preferred (palonosetron)
- Delayed → NK_1R $\ominus$ → - Pitant (Netupitant)

Specific Adverse Effects 00:05:05

- Cyclophosphamide
  Ifosfamide
  Vinca
  } SIADH
  (Vinca > phosphomide)
  ↓
  Rx: - Tolvaptan (P.O)
  Conivaptan (i.v)

↓
Hemorrhagic cystitis
↓
Ifosfamide > cyclophosphamide
↓

- Rx: -
  - Adequate hydration
  - MESNA

EMESIS (WITH CISPLATIN)

- Rx: - Palanosetron + Netupitant)
  - Neurotoxicity
  - Nephro → prevent:- Amifostine
  - Ototoxicity

6-TG/6-MP

- Hepatotoxicity
- Squamous cell Ca

  ↓
- R_X: - cemiplimab

MT_X (METHO TREXATE)

- Mucositis → R_X: - Palifermin
- BMD → R_X: - Folinic acid /Leucovorin
- Renal toxicity → R_X :- Hydration and urinary alkalinisation
- Poisoning → R_X: - Glucarpidase

Hand & Foot Syndrome 00:10:08

- 5-FU
- Capecitabine
- Demetrexed
- Doxorubicin
- R_X: -
  - Dexamethasone
  - Cobalamine

Gemcitabine/Irinotecan

- Diarrhea

  ↓
- R_X: - Racecadotril

ARABINE DRUGS → Ataxia & Arthralgia

- Cytarabine → Cerebellar ataxia
- Fludarabine → Arthralgia

Drugs Causing Pulmonary Fibrosis 00:12:30

- NICC BABE
- Ni → Nitrofurantoin
- CE → Cyclophosphamide
- B → Busulfan
- A → Amiodarone
- B → Bieomycin
- E → ergot derivatives

Drugs Not Causing BMD

Mnemonic: "Para tine bleo tin"

- Asparagine
- Vincristine
- Bleomycin
- Cisplatin

Anthracyclines

- Cardiotoxicity – produces iron free radicals that interact with myocytes

↓

- R_X: – Dexrazoxane – chelates iron

Somustine

- Renal Failure

"Tine + tax causes pain in the ass"

• Vincristine • Paclitaxel • Docetaxel	stocking & glove neuropathy

Taxanes

- Maximum alopecia

SMALL MOLECULE INHIBITORS

- These small molecular are responsible for any kind of repair process to occur in abnormal cells
- If we stop the repair process especially in the cancer cells the cells will be destroyed

Proteasome inhibitor 00:00:44

Protein for degradation
↓
Proteasome
↓
Inhibited by proteasome inhibitor →

"some"
↓
"zome"
↓
Bortezomib
Carifilzamib

- R_X: -
  - Multiple myeloma
  - Carcinoma pancreas

- Adverse effects
  - GI
  - PN (Peripheral neuropathy)

- Reactivates latent Herpes infections

Histone-De-Acetylase Inhibitor 00:02:40

Histone

Acetylated
↓
Increases binding of histone
↓
Stabilizes DNA

De-acetylated
↓
Stimulates for transcription
↓
Protein synthesis

- De-acetylation (-)

  Histone deacetylase inhibitor
  - Vor inostat
  - Belinostat
  - Panobinostat
  - Depsipeptide
  - Sodium valproate
- De-acetylase stimulated by: - Theophylline
  - VORINOSTAT → R_x: - of cutaneous T-cell lymphoma

    ↓

    "Weight loss"

PARP- Inhibitors: - 00:05:58

(Poly ADP ribose polymerase)

Damaged DNA

↓

PARP activated

↓

Attempt for repair

PARP Inhibitors: -

"Par"

↓

Olaparib

Rucaparib

- Ca-ovary, breast

- Adverse: - BMD (bone marrow depression)

CDK - 00:07:24

CDK

↓ (prevent alopecia) can be administered along with taxanes

- PALBOCICLIB
  - ER (+) advanced Ca breast
  - Given along with Fulvestrant (for Tamoxifen resistant Ca breast)
- Ribociclib
  - Adverse effects

i. BMD

ii. Pulmonary embolism

Apoptosis inducers 00:09:11

- Ingenol mebutate
- R_X: - topical for actinic keratosis

TARGETED THERAPIES

Conventional therapies

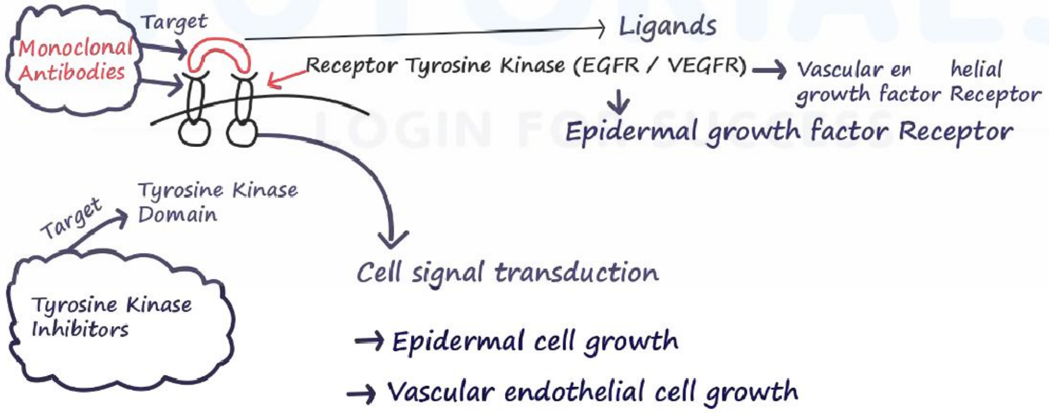
Disadvantages

- i. Non – Specific
- ii. Ineffective in slow growing tumors
- iii. Increased resistance – Due to
  - a. Increase DNA repair mechanism
  - b. Inactivation
  - c. Expulsion of drug & prevention of accumulation & thus preventing its action

---

Targeted therapies 00:03:48

Tyrosine Kinase


Monoclonal Antibodies
Target
Ligands
Receptor Tyrosine Kinase (EGFR / VEGFR)
Vascular endothelial growth factor Receptor
Epidermal growth factor Receptor
Target
Tyrosine Kinase Domain
Tyrosine Kinase Inhibitors
Cell signal transduction
→ Epidermal cell growth
→ Vascular endothelial cell growth

MAB

Drug	Target	Uses
Cetuximab	EGFR (HER – 1)	Advanced colo rectal carcinoma Head & Neck carcinoma
Tratuzumab	EGFR (HER-2)	Ca Breast Ca Stomach
Bevacizumab	VEGF	Colorectal Ca Lung Glioblastoma Kidney HER 2-ve breast Cervical Ovarian

TKI

Drug	Target	Uses
Imatinib	BCR/ABL C-Kit	CML/ALL GISTs
Erlotinib, Gefitinib	EGFR (HER-1)	Non-small cell lung carcinoma
Lapatinib Neratinib	EGFR (HER-2)	Breast
Sunitinib	VEGFR	GISTs, RCC
Sorafenib	VEGFR	RCC, HCC, Thyroid
Lenvatinib	VEGFR	Thyroid, RCC

Disadvantages

- Can be used in cells with target proteins
- Normal cells expressing those receptors are also damaged

Adverse reaction

MAB

Skin reactions

TKI

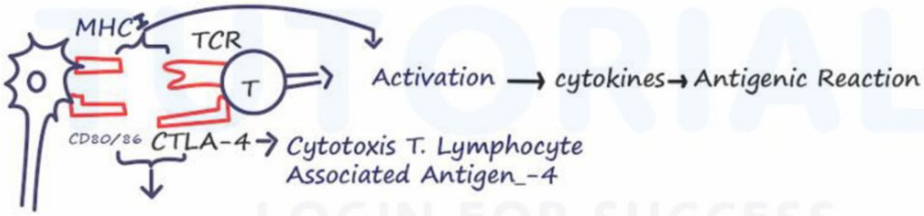
↓

Hematological conditions

↓

Anemia, neutropenia

Immune check point therapy 00:15:50

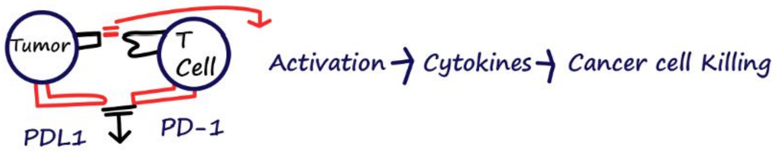

MHC
TCR
T
Activation → cytokines → Antigenic Reaction
CD80/86
CTLA-4 → Cytotoxis T. Lymphocyte Associated Antigen_-4

Activation of T cells does not occur

↓

The mechanism is utilized to

Prevent Autoimmune reaction


Tumor
T Cell
Activation → Cytokines → Cancer cell Killing
PDL1
PD-1

Programmed cell

Death protein 1/ligand

↓

No activation

↓

∴ Cancer cell survives

Drug	Target	Uses
Ipilimumab	CTLA-4	Melanoma, RCC, Colorectal
Pembrolizumab	PD-1	Melanoma Non-small cell lung carcinoma (NSCLC) Head & neck squamous tumors Hodgkin's lymphoma
Nivolumab	PD-1	Melanoma, Lung Ca, RCC
Atezolizumab	PDL-1	Urothelial Ca, Bladder Ca
Avelumab	PD-L-1	Merkel cell Ca, Urothelial Ca, RCC
Lenvatinib	VEGFR	Thyroid, RCC
Durvalumab	PDL1	Bladder Ca, NSCLC
Cemiplimab	PD-1	Cutaneous small cell Ca

FDA Approved Combination therapies

Drugs	Indications
Bevacizumab + Carboplatin + Paclitaxel	NSCLC
Bevacizumab + 5 FU	Colorectal Ca
Bevacizumab + Atezolizumab	Non – Squamous NSCLC
Lenvatinib + Pembrolizumab	Advanced endometrial Ca

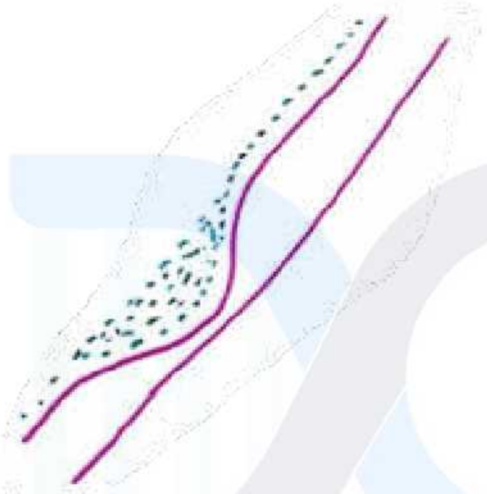
PEPTIC ULCER DISEASE - I

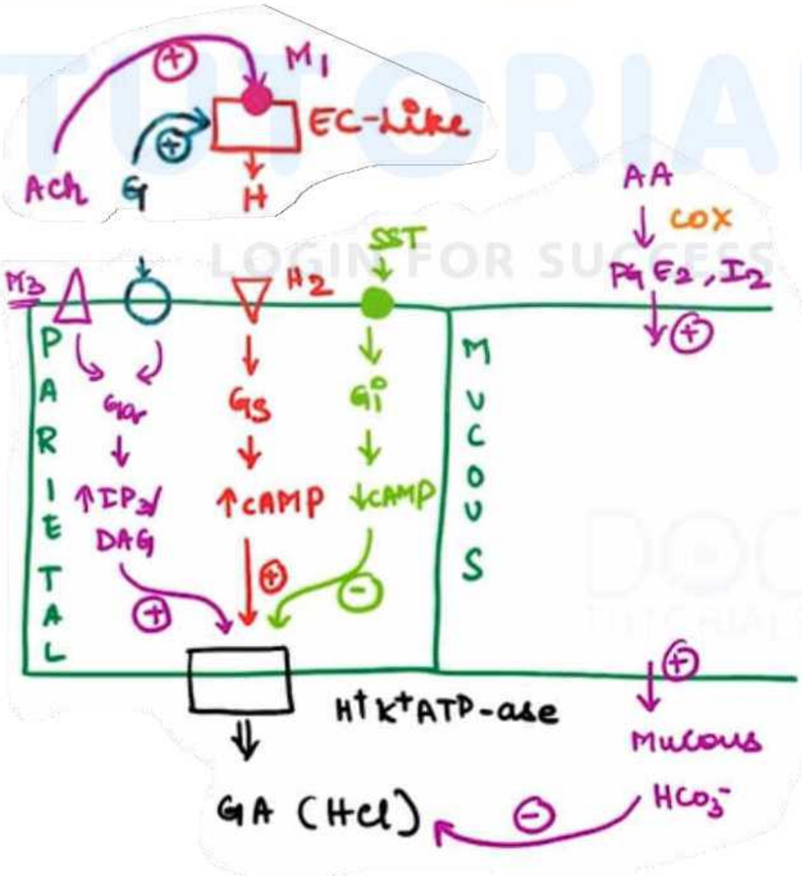
Gastro Intestinal trait 00:00:14

Blood

Enterochromaffin like cell

Histamine




+
M1
EC-Like
+
Ach
G
H
AA
COX
SST
PG E2, I2
M3
H2
+
PARIETAL
Gq
Gs
Gi
↑IP3/DAG
↑cAMP
↓cAMP
MUCOUS
+
+
−
+
H⁺K⁺ATP-ase
Mucous
GA (Hcl)
−
HCO3⁻

Lumen

- H+ K+ ATPase – Pump helps in secreting Gastric acid
- An enterochromaffin like cell is present that secretes histamine, this histamine H_2 acts as parietal cell as a receptor
- This GS coupled receptor further increases cyclic AMP which in turn increases gastric acid production
- Gastrin will act on its own receptors and acetyl choline will act on M3 receptors
- Both of these are GQ receptors that tends to increase the IP3/DAG to cause inhibition of gastric acid secretion
- In mucous cell the arachidonic acid forms P4E2, I2 with the help of cyclooxygenase enzyme
- This PGE2 & I2 enhances the production of mucous & Bicarbonate (HCO-3)

H2 blockers 00:07:00

Highly selective agents

- Lamtidine
- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine - 100% (Peroral Bioavailability)

Nizatidine

Causes	MOA
- Gastric acid decreases	- Competitive blocker
- Pepsin decreases	- Nocturnal > Meal stimulated

- Used in prevention of pre-operative aspiration induced pneumonia

CIMETIDINE

- Acts as **microsomal enzyme inhibition**
- Decreases hepatic blood flow

Adverse effects

- Gynecomastia
- Loss of libido
- Displace AHT from cytoplasmic receptors

FAMOTIDINE

- In histamine → This drug behaves as competitive antagonist
- In absence of histamine – Inverse agonist agent

PPI – PROTON PUMP INHIBITORS 00:10:01

- **Dose depended acid suppression** (Both resting & meal stimulated)

- No effect or pepsin, intrinsic factor, juice volume and GI motility

Mechanism of action

- In the parietal cell villi are present on the villi are present H^+ K^+ ATPase pump
- In blood vessels protons are present that move into the parietal cell and gets ionized and moves into the villi
- These ionized cells inhibit the H^+ K^+ ATPase pump & inhibition of carbonic acid enzyme

PPI's Omeprazole

- More acid labile
- Bioavailability is decreases with food
- It is taken on empty stomach
- It gets absorbed and concentration is high after 7 hours
- Actively secreting proton pumps are inhibited

MOST STABLE ACID DRUGS

- Tenatoprazole > Pantoprazole > Omeprazole > Lansoprazole > Rabeprazole

Rabeprazole fast acting

- Hit & run → Non-competitive & irreversible
- H^+ K^+ run → ATPase

↓

- Reactivation half time – 18hrs
- Omeprazole – inhibits CYP2C allows CYPIA
- Inhibition CYP2C leads to activation of clopidogrel
- This drug increases the levels of diazepam, phenytoin
- Lansoprazole is safer, inhibition is partly reversible

Adverse drug reactions

- Atrophic gastritis
- Competitive – Hypergastrinemia
- Gynaecomastia/Erectile dysfunction
- Increased respiratory GI infections
- Development of osteoporosis

AmoTahseeh.com
TUTORIALS
LOGIN FOR SUCCESS

PEPTIC ULCER - II

- Two important group of Drugs

Anticholinergic Agents 00:00:14

- PIRENZEPINE
  - Enteric system with which we can identity this drug is going to be utilized in decreasing the gastric acid secretion
  - Classical features (not used, as proton pump inhibitors are preferred)
  - Decreases acid volume, no change in pH

Prostaglandins → Misoprostol 00:01:16

- They reinforce the mucous layer/HCO_3^-
- They are cytoprotective, no effect on decreasing the gastric acid, it alters the pH

Antacids 00:02:04

- Increases pH more than 4
- It has two major mechanisms
  i. Antagonizes gastric HCl
  ii. Reflux gastrin release
  iii. In reflux release
- Causes acid rebound increase in gastric motility
- Calcium carbonate is maximum in gastric motility

Salient features of Antacids

- Most efficacy drug → Magnesium hydroxide
- Most Potent → Calcium carbonates
- Aluminum and Magnesium salts

Aluminum salts ↓ Causes minimum Stools ↓ Constipation (Smooth muscle relaxant) Mucosal antigen

Magnesium salts ↓ Easy Stool ↓ Diarrhea (laxative)

- Aluminum and magnesium is contraindicated in Renal failure

Sucralfate 00:04:41

- When gastrointestinal mucosa is damaged, the gastric acid which is secreted is constantly interacting with cells beneath them because of which patient is feeling pain

Sucralfate is aluminum salt of sucrose

↓

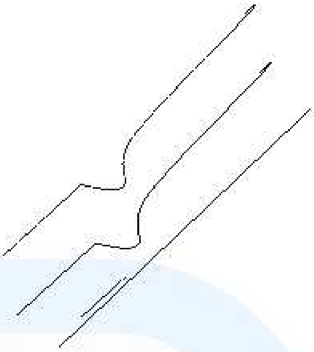
After ingestion changes into paste like substance only when the pH is less than 4

↓

When pH is less than 4, it gets deposited on the affected area

↓

Coated in the Mucosa



- Sulfate→ Aluminum paste of sucrose → Conversation to paste like (PH<4)
- It only changes into paste in acidic PH. If patient is treated with proton pump inhibitor like omeprazole & given sulfate simultaneously in treatment it will not change into paste like substance because the gastric acid PH is not going to be less than 4
- Because of proton pump inhibitor, Acid pH changes into alkaline pH
- Sulfate +PPI/H_2RA → Combination irrational
  - Additional Point
    - i. It delay's gastric emptying
    - ii. Hypophosphatemia
    - iii. Constipation

H. Pylori 00:08:32

- Two types of treatment
  i. Low clarithromycin resistance
  ii. High clarithromycin resistance

Low clarithromycin resistance	High clarithromycin resistance
Triple therapy regimen ↓ CAP C – Clarithromycin – 500mg BD A – Amoxicillin – 100mg BD P – PPI – Lansoprazole – 30mg BD	Quadruple therapy regimen ↓ BOTM B – Bismuth subcitrate -120mg QID O – Omeprazole – 20mg BD T – Tetracycline – 500mg QID M – Metronidazole – 400mg TDS

- Both of the regimen is treated for two weeks

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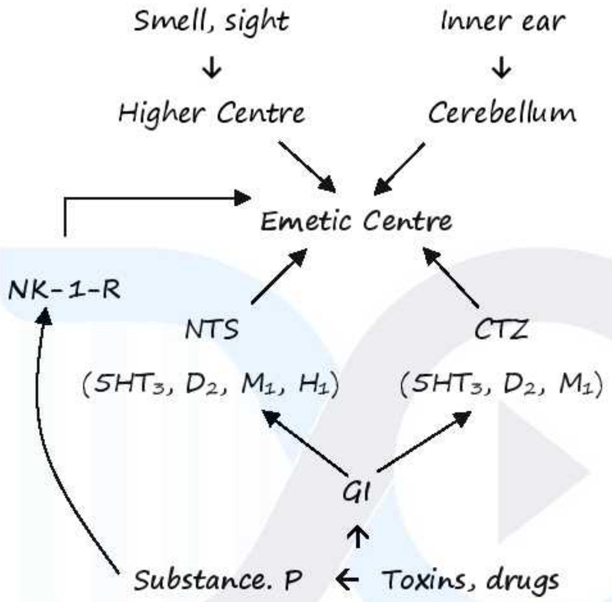
DRUGS FOR ANTI-EMESIS, CONSTIPATION AND DIARRHOEA

Anti-emetics 00:00:14


Smell, sight
Inner ear
Higher Centre
Cerebellum
Emetic Centre
NK-1-R
NTS
(5HT3, D2, M1, H1)
CTZ
(5HT3, D2, M1)
GI
Substance. P
Toxins, drugs

Treatment

Prokinetic agents

- Promethazine → Dystonia ← Metoclopramide
- Cisapride → arrhythmia QT-prolong

Mechanism of action of prokinetic drugs	
Drug	**Mechanism**
Metoclopramide	D2⊖ 5-HT4⊕
Domperidone	D2⊖
Cisapride	5-HT4 ⊕ Weak 5-HT3⊖

Mosapride	5-HT4 ⊕ 5-HT3 ⊖
Itopride	D2 ⊖ Anti ChE Weak 5-HT4⊕
Levosulpride	D2⊖ Atypical anti-psychotic Anti-emetic
Cinitapride	5-HT2⊖ D2⊖ 5-HT4⊕

New anti-emetic

CB_1-R
↓
Dronabinol
Nabilone
↓
Sedation
Tacty
Increase appetite
Blood shot eyes

NK-1-R
↓
Aprepitant
Fosaprepitant (iv)
Rolapitant (iv)
Netupitant
Fosentupitant (iv)

Adverse effects
Diarrhea
Fatigue
CYP3A4

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CIE (Chemotherapy induced emesis) → $5HT_3$⊖ + NK-1-R⊖ + steroid

(palono) (Netu)

- CIE → most potent (Palono)
  - Most specific (Grani) T.D
- Morning sickness: Doxylamine + vitamin B6

Constipation

00:12:48

Laxatives

Bulk forming	**Stimulants**	**Emollients**	**Hyper osmotic**
↓ High fibre	↓ Increases peristalsis	↓ Stool softener	↓ Increased fecal water content
Example: Psyllium Methyl cellulose Poly carbophil	**Example:** Caster oil Senna Bisacodyl	**Example:** Mineral oil (Liquid paraffin) docusate	**Example:** PEG Sorbitol Glycerin Lactulose
↓ **Adverse effects:** Impaction Fluid overload	↓ **Adverse effects:** Nutrient malabsorption Melanosis coli (senna and Bisacodyl)	↓ **Adverse effects:** Rash Decreased fat soluble vitamin absorption	↓ **Adverse effects:** Bowel distention

Irritation

Electrolyte disturbances

- 5HT4 agonist
  - Cisapride
  - Mosapride
  - Prucalopride

Increases G_1 motility (chronic)

Diarrhea 00:19:26

- Absorbances
  - Bismuth dub salicylate
  - Kaalin – Pectin
  - Activated charcoal
  - Attapulgite

Increase BT (with anti coag)
Constipation
Dark stools (BSC)

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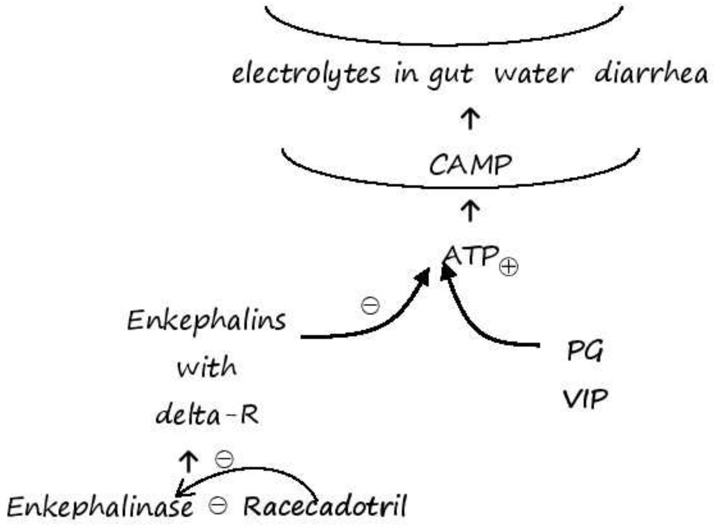
Opiates

- Increase GI motility
- Increases transit time
  - Water, electrolytes reabsorption time increased
- Loperamide
  Codeine
  Paregoric
  Diphenoxylate


electrolytes in gut water diarrhea
CAMP
ATP ⊕
Enkephalins
with
delta-R
⊖
PG
VIP
⊖
Enkephalinase ⊖ Racecadotril

Advantages

- Drowsiness
- N/V/constipation
- Brady

Racecadotril

- P.O
- Acute secretory diarrhea (also octreotide)
  - No change in transit
  - No bloating
  - No abdominal pain
  - No constipation

- Crofalemer → AIDS ← non-infections diarrhea
- Telotristatethyl → Carcinoid diarrhea

DRUGS FOR BRONCHIAL ASTHMA

Bronchial Asthma
↓
Antigen
↓ (induce)
Lymphoid tissue
↓
Production of specific IgE antibodies
Y Y
↓
Expressed on surface of mast cells
↓
It interacts with antigen
↓
Degranulation of mast cells

DOC TUTORIALS
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Leukotrienes
↓
Bronchoconstriction
(Wheezing)
↑ ⊖
Relievers
(∴ Relieve Bronchoconstriction)

1. Beta 2 Agonist
   - SABA (Short Acting β_2 Agonist)

- Bronchial hyperreactivity
- Mucus plugging

↓
Inflammation
↑ ⊖
Controllers
(Control Inflammation)

1. Steroids
2. Omalizumab (against IgE Antibody)

- LABA (Long Acting β_2 Agonist)

2.Anticholinergic

3.Theophylline (Methyl xanthines)

OM – Asthma

ALI – Inhibit products of lymphoid tissue

MAB – Monoclonal Ab

3.Cromolyn sodium

Leukotrine receptor antagonistic agent
5-Lipoxygenase inhibitor

These have both effects. (i.e. controllers & relievers)

Drug Induced Bronchospasm 00:06:45

1.Aspirin

2.Non selective betablockers

(Block Beta Receptors on bronchial smooth muscle & this cause Bronchoconstriction)

Note (β_2 → Bronchial smooth muscle relaxantants
↓
GS

(M_3 – Bronchial smooth muscle (BSM)
↓ ↓
(Gq Receptor) cause Bronchoconstriction

3.Cholinergic drugs

4.Tubocurarine

5.Zanamivir (Antiviral – Antifluenza drug)
(given via Inhalational route)

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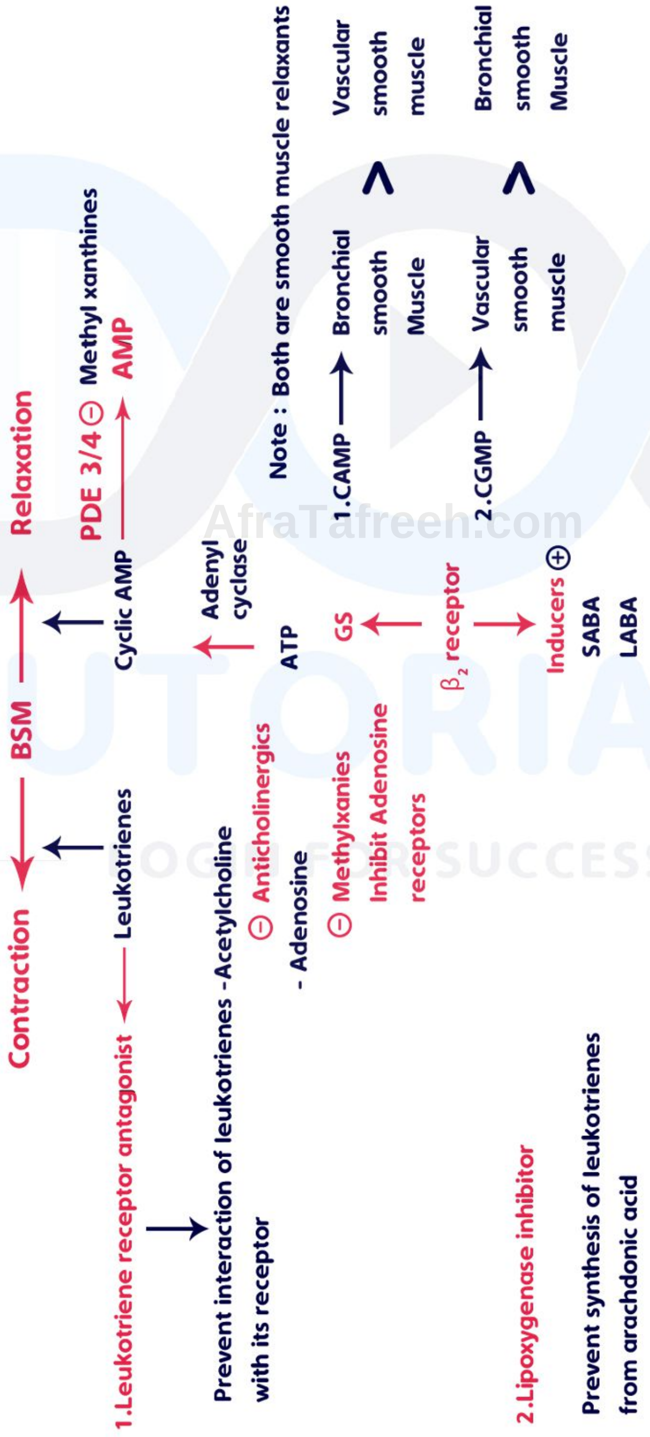
Relievers 00:09:00

- Note – for PSVT with bronchial asthma Adenosine is contraindicated
  DOC – Cardio selective calcium channel blockers eg. Verapamil & Diltiazem


Contraction
BSM
Relaxation
Leukotrienes
Cyclic AMP
PDE 3/4 ⊖ Methyl xanthines
AMP
1.Leukotriene receptor antagonist
Prevent interaction of leukotrienes with its receptor
Adenyl cyclase
ATP
-Acetylcholine
⊖ Anticholinergics
- Adenosine
⊖ Methylxanies
Inhibit Adenosine receptors
GS
β2 receptor
Inducers ⊕
SABA
LABA
Note : Both are smooth muscle relaxants
1.CAMP → Bronchial smooth Muscle > Vascular smooth muscle
2.CGMP → Vascular smooth muscle > Bronchial smooth Muscle
2.Lipoxygenase inhibitor
Prevent synthesis of leukotrienes from arachdonic acid

Beta 2 (β_2) agonistic agents 00:18:27

β_2 Agonists

↓

β_2 Stimulation

+

Decreases release of mediators

+

Increases Mucociliary clearance

Note:

Anticholinergic decrease mucociliary clearance

↓

Atropine> Iprotropium bromide

↓

Used in Asthma

Drugs – 2020

SABA

Non Selective
- Adrenaline
- Isoprenaline

Note – Nor Adrenaline low

Low β_2 action

Selective
- Salbutamol
- Albuterol
- Terbutaline
- Perbuterol
- Metaproterenol

↓

Used for non responsive bronchial asthma

LABA
- Salmeterol
- Formoterol ← faster onset of action
- Indaceterol
- Velanterol
- Olodaterol
- Bambuterol

↓

- Per oral route
- It is a prodrug

↓

Enters lungs & get converted to active

Form(Terbutaline)
by
pseudocholinesterase
It is ester drug

Adverse Effects 00:24:44

3T's

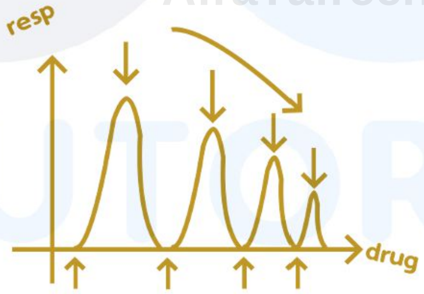
1.T – Tremors

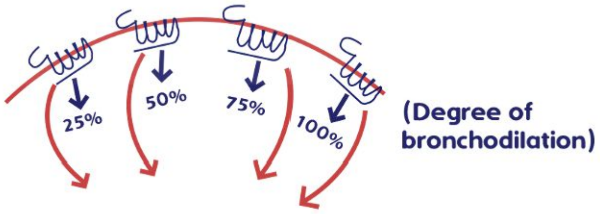
2.T – Tachycardia (β_2 Stimulation in cardiac muscle)

Increased dose leads to action on

B_1 also leading to tachycardia

3.T – Tachyphylaxis





Repeated stimulation leads
Internalization & destruction of receptors.
Leading to loss of effect of drug

- Note – Steroids prevent internalization and thus tachyphylaxis.

→ They also induce synthesis of new β_2 receptors.

4.Hypokalemia:

Note: Betablockers produce Hyperkalemia

Methl Xanthines 00:31:58

Methyl Xanthines

Purine Derivatives

- Caffeine (better than theophylline)
- Theobromine

Lipid soluble drugs
↓
Cannot be given parenterally
∴Extravasation occurs ∴ peroral

- Aminophylline
- Oxtriphylline

Water soluble
Can be given (IV)

Non purine derivatives

- Roflumilast [PDE – 4⊖]

MOA

1.PDE 3/4 ⊖ (also known as non specific PDE inhibitor)

2.Adenosine receptor antagonist (Type 1 receptor ⊖)

3.Anti-inflammatory property

4.Increase apoptosis of granulocytes

5.Histone deacetylase activator agent (HDA)

Note: HDA Inhibitor
↓
Vormostat (anti cancer drug)
Balenostat
Valproate

Adverse Effects 00:36:37

I. Vomitting /Nausea
Headache
GI Discomfort
] PDE 4 ⊖

II. Diuresis/seizures → Adenosine 1 receptor antagonistic property

III. Cardiac arrthymia → PDE 3 Inhibition
+
Adenosine type 1 receptor inhibition

- Therapeutic concentration: 5-15 mg/L
- Bronchodilation >10 mg/L
- Theophylline is metabolized by microsomal enzymes
  - Inhibition: Prolongs action of theophylline
  - Stimulation: Decreases action of theophylline

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Effects

Increased by		Decreased by
- Erythromycin	Microsomal Enzyme Inhibitors	- Phenytoin
- Ciprofloxacin		- Smoking
- Cimetidine		- Phenobarbitone
- Allopurinol		- Rifampicin
- Vaccination		- Charcoal boiled meat
- High Carbohydrate duct		- Young age

- High protein diet
- Low carbohydrate diet

- [It is used for apnoea in premature infants ∴ It stimulates respiratory center]

  Note: Azithromycin has low microsomal inducing property.

Anticholinergics

1. Ipratropium Bromide → Quaternary amine (ionized drugs)

   ↓

   Can produce paradoxical bronchoconstriction due to additive molecule in it.

   ↓

   Non penetrable drug (least adverse effects)

   ↓

   Remain with in alveoli & produces bronchodilation

   - Teritiary amines are lipid soluble & can cross lungs to enter blood stream if given via inhalation.
2. Tiotropium bromide: long acting
3. Revefenacin – long acting muscarinic agent

   The above drugs are better in COPD > BA

Controllers 00:46:44

Glucocorticoids

- Inhalational route is better to avoid adverse effects.

Inhalation —
- Beclomethasone
- Budesonide
- Flunisonide
- Ciclesonide
- Prednisonide → per oral

MOA

- Acute Bronchial Asthma: Increase sensitivity of β_2 receptor
- Chronic Bronchial Asthma: Anti inflammatory property.

Adverse Effects 00:48:36

1. Oropharyngeal candidiasis/ Hoarseness of voice

   Prevention

   i. Gargling after using drugs via MDI

   ii. Spacer

Note: Disadvantage of MDI Leads to deposition aof drug in pharynx, if not used properly.

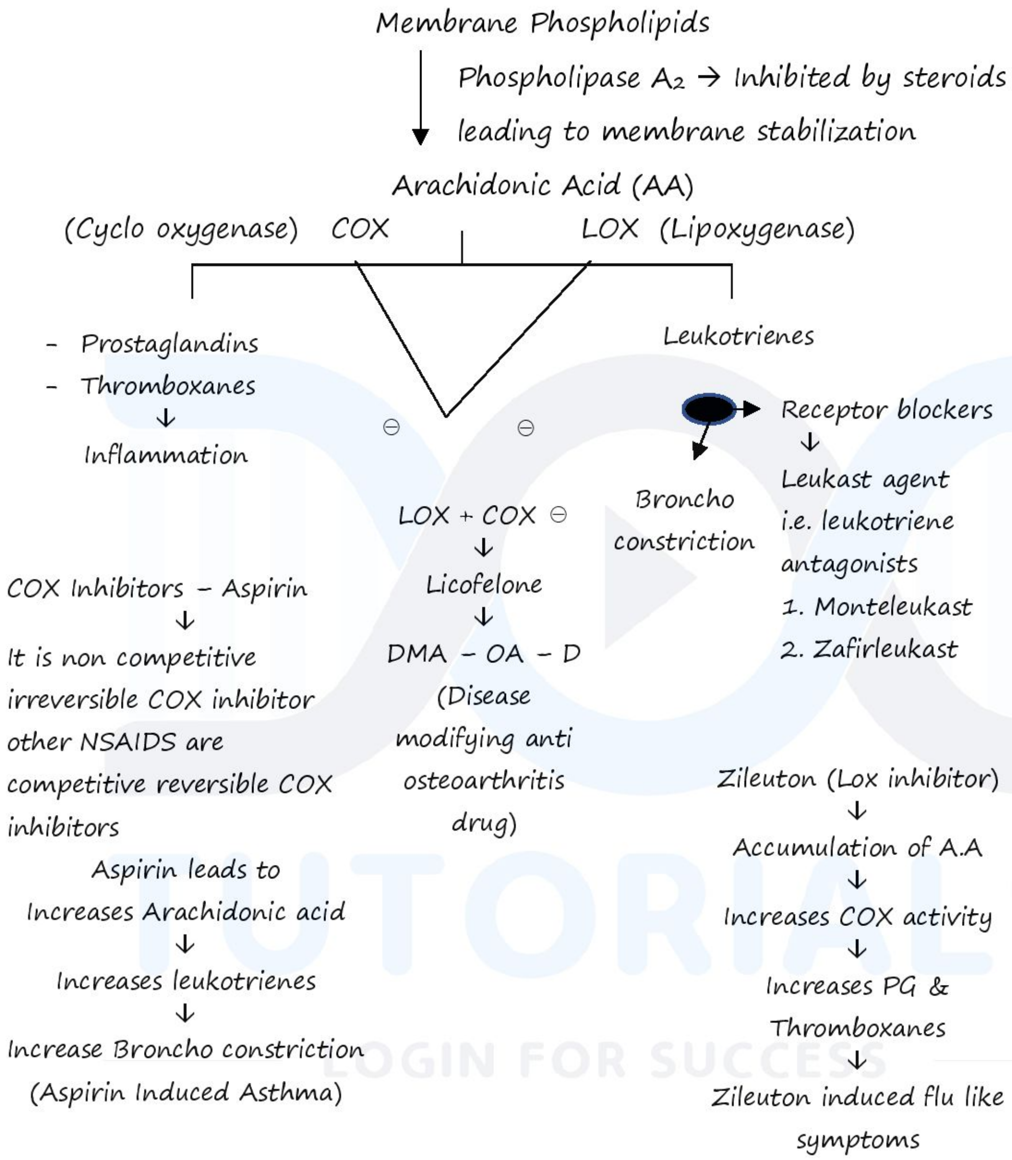
2. Pulmonary TB (Due to immunosuppression caused by long standing use of steroids)
3. Rare

   a. Adrenal suppression

b. Osteoporosis (more common with systemic corticosteroids)

4. In children – Growth retardation

Leukotriene Inhibitor



Membrane Phospholipids

Phospholipase A_2 → Inhibited by steroids leading to membrane stabilization

Arachidonic Acid (AA)

(Cyclo oxygenase) COX

LOX (Lipoxygenase)

- Prostaglandins
- Thromboxanes

↓

Inflammation

Leukotrienes

Receptor blockers

↓

Leukast agent i.e. leukotriene antagonists

1. Monteleukast
2. Zafirleukast

Broncho constriction

⊖ ⊖

LOX + COX ⊖

↓

Licofelone

↓

DMA – OA – D

(Disease modifying anti osteoarthritis drug)

COX Inhibitors – Aspirin

↓

It is non competitive irreversible COX inhibitor other NSAIDS are competitive reversible COX inhibitors

Aspirin leads to

Increases Arachidonic acid

↓

Increases leukotrienes

↓

Increase Broncho constriction

(Aspirin Induced Asthma)

Zileuton (Lox inhibitor)

↓

Accumulation of A.A

↓

Increases COX activity

↓

Increases PG & Thromboxanes

↓

Zileuton induced flu like symptoms

Leukotrienes Inhibitor Types 00:58:39

Leukotriene inhibitors

Receptor Antagonists
↓
- Montelukast
- Zafirlukast

↓
Blocks
- LT D_4 receptor
- LT C_4 receptor

It does not block
LT – B_4 receptor
↓

5-LOX inhibitor
↓
- Zileuton

↓
May produce
- Hepatotoxicity
- Flu like symptoms

- Might develop churg-strauss syndrome (vasculitis with eosinophilia)
- Might produce montelukast
  - Adult – Headache
  - Children – Agitation (Neuropsychiatric disturbance)
  - Cycloserine – antibiotic inhibits cell wall
  - Mefloquine – antimalarial

May also produce neuropsychiatric disturbances.

Anti IgE and Cromolyn 01:03:45

Anti – IgE	Cromolyn
↓ - Omalizumab ↓ Approved for > 12 years age Given → SC	↓ - Nedocromil - Sodium cromoglylcate ↓ Acidic agents ↓ a.k.a mast cell stabilizers ↓ Can be used for prophylaxis

- Other Stabilizers in pharmacology
  - Mood stabilizers → lithium
  - Serotonin dopamine stabilizers → Aripiprazole

- Other monoclonal antibodies approved for bronchial asthma: (add on therapy for bronchial asthma)

i. Anti – IL 5 antibody → Mepolizumab, reslizumab

ii. Anti – IL 5 R antibody → Benralizumab

iii. Anti – IL 4 R antibody → Dupilumab.

DRUGS FOR COUGH

We have two different types of coughs

i. Dry cough

ii. Productive cough

Dry cough

- Antitussives are used for dry cough.

Antitussive agents 00:01:02

Opioids

- Codeine
- Hydrocodine
- Pholcodine
- Opioids decrease the sensitivity of cough Centre
- Opioids are no longer used they are banned because of a condition called Opioid Use disorder (OUD)

Dextromethorphan 00:01:02

- It is a levo-isomer of opioid.
- It is used for dry cough.
- It can be used in ALS (amyotrophic lateral sclerosis)
- It can be used in pseudo bulbar affect disorders

  In both ALS and pseudo bulbar affect disorders dextromethorphan acts as an NMDA antagonistic agent, it is given along with quinidine (here quinidine acts as microsomal inhibitor drug)

- By inhibiting microsomal enzymes dextromethorphan accumulates and due to accumulation, it has more amount of CNS accumulation leading to NMDA antagonistic activity (not seen in regular intake of low doses)

Levocloperastine 00:03:12

- It is non-opioid antitussive agent.
- It blocks both central and peripheral causes of cough
- Central - it suppresses the cough Centre.
- Peripheral - it also blocks receptors on bronchus

Productive cough

- Expectorants are utilized for productive cough.
- Expectorants are also called as mucolytic agents.

The different expectorants we have are

i. Bromhexine

ii. Ambroxol

iii. Potassium iodide (KI)

iv. Guaifenesin (expectorant activity only at high doses)

v. N-acetyl cysteine

- N-acetyl cysteine is the drug of choice for the treatment of Paracetamol poisoning.

DRUGS FOR GLAUCOMA

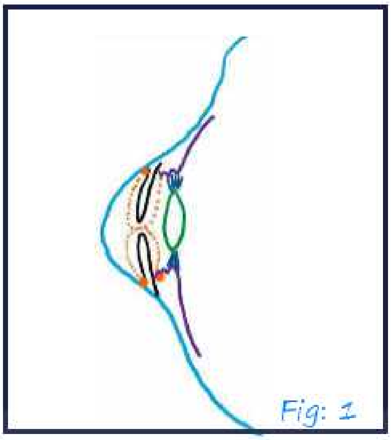


Fig: 1

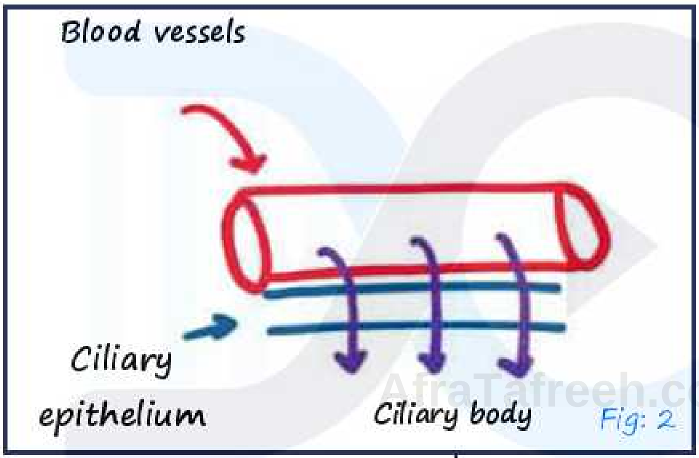

Blood vessels
Ciliary epithelium
Ciliary body

Fig: 2

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↓

Aqueous humour

(hydrostatic pressure & active transport)

↓

Posterior chamber

↓

Anterior chamber

PGF2α analogue	Uveoscleral outflow
(minor) +	(major) (20-40%) +
↓	↓
Trabecular meshwork	Passes thro uveal meshwork
	↓

(60-80%)
↓
Passes thro
1. Uveal
2. Corneoscleral
3. Juxta canalicular
↓
Schlemm's canal
↓
Conjunctival episcleral veins

Supra choroidal space
↓
Scleral & conjunctival veins

Drains back into systemic circulation

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i. Acetazolamide
ii. Dorzolamide
iii. Brinzolamide

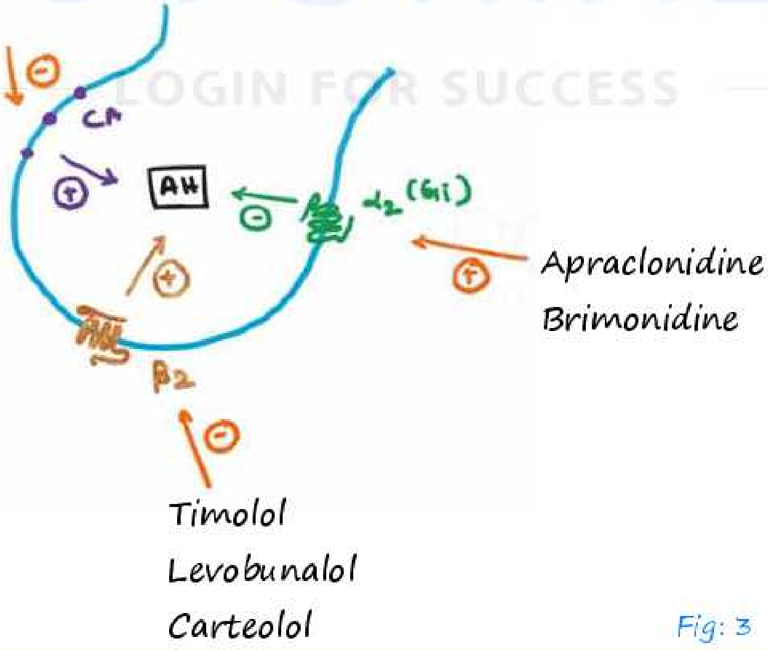
⊖
CA
⊕
AH
⊖
α_2 (Gi)
⊕
Apraclonidine
Brimonidine
⊕
β_2
⊖
Timolol
Levobunalol
Carteolol

Fig: 3